

1 5-[PHENYL, TETRAHYDRONAPHTHALENE-2-YL
2 DIHYDRONAPHTHALEN-2-YL AND HETEROARYL-CYCLOPROPYL]-
3 PENTADIENOIC ACID DERIVATIVES HAVING SERUM GLUCOSE
4 REDUCING ACTIVITY

5 BACKGROUND OF THE INVENTION

6 Field of Invention

7 The present invention relates to compounds that have the property of
8 reducing serum glucose and serum triglyceride levels in diabetic mammals without
9 the undesirable properties of reducing serum thyroxine levels and transiently
10 raising triglyceride levels. More particularly, the present invention relates to 5-
11 [phenyl, tetrahydronaphthalene-2-yl dihydronaphthalen-2-yl and heteroaryl-
12 cyclopropyl]-pentadienoic acid derivatives having the above-noted biological
13 property.

14 Compounds that have retinoid-like activity are well known in the art, and are
15 described in numerous United States and other patents and in scientific
16 publications. It is generally known and accepted in the art that retinoid-like
17 activity is useful for treating animals of the mammalian species, including humans,
18 for curing or alleviating the symptoms and conditions of numerous diseases and
19 conditions. It is now general knowledge in the art that two main types of retinoid
20 receptors exist in mammals (and other organisms). The two main types or families
21 of receptors are respectively designated the RARs and RXRs. Within each type
22 there are subtypes; in the RAR family the subtypes are designated RAR_{α} , RAR_{β}
23 and RAR_{γ} , in RXR the subtypes are: RXR_{α} , RXR_{β} and RXR_{γ} . It has also been

1 established in the art that the distribution of the two main retinoid receptor types,
2 and of the several sub-types is not uniform in the various tissues and organs of
3 mammalian organisms. Moreover, it is generally accepted in the art that many
4 unwanted side effects of retinoids are mediated by one or more of the RAR
5 receptor subtypes. Accordingly, among compounds having agonist-like activity at
6 retinoid receptors, specificity or selectivity for one of the main types or families,
7 and even specificity or selectivity for one or more subtypes within a family of
8 receptors, is considered a desirable pharmacological property.

9 For a general overview of the retinoid receptors see *Mangelsdorf et al.* (1994)
10 *The Retinoid Receptors In: The Retinoids*, edited by *Sporn et al.* p 319-349. Raven
11 Press, Ltd., New York. For another general overview see *Dawson and William H.*
12 *Okamura*, *Chemistry and Biology of Synthetic Retinoids*, published by CRC Press
13 Inc., 1990, pages 324-356.

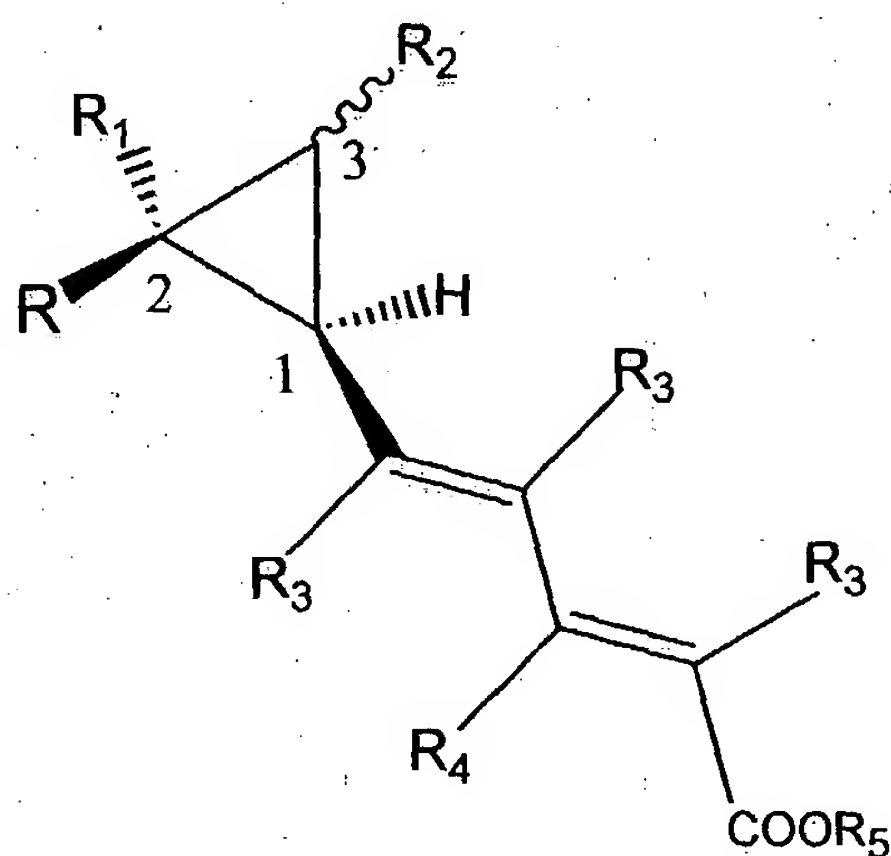
14 The following United States patents disclose compounds that include a
15 pentadienoic acid moiety attached to a cyclopropyl group, with retinoid or like
16 biological activity: U. S. Patent Nos. 6,403,638; 6,147,224; 6,034,242; 6,048,873;
17 6,147,224; 5,917,082 and 5,675,033.

18 Relatively recently it has become known that certain retinoid compounds are
19 capable of reducing serum glucose levels in diabetic mammals. Mukherjee, R.;
20 Davies, P. J.; Crombie, D. L. Bishoff, E. D.; Cesario, R. M.; Jow Hamann, L. G.;
21 Boehm, M. F.; Mondon, C. E.; Nadzan, A. M.; Paterniti, J. R. Jr.; Heyman, R. A.
22 Sensitization of Diabetic and Obese Mice to Insulin by Retinoid X Receptor
23 Agonists, *Nature* **1997**, 386 (6623), 407-410. The compound (2*E*, 4*E*, 1'*S*, 2'*S*)-3-

1 methyl-5-[2'-methyl-2'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-
 2 cyclopropyl]-penta-2,4-dienoic acid, described in United States Patent No.
 3 6,114,533, has this property. A disadvantage of the prior art retinoid compounds
 4 that reduce serum glucose levels is that their administration usually also results in
 5 the pharmacologically undesirable reduction of serum thyroxine levels and a
 6 transient increase in serum triglyceride levels. The present invention is directed to
 7 novel compounds which do not have these undesirable side effects.

8 SUMMARY OF THE INVENTION

9 The present invention relates to compounds of **Formula 1**



10 Formula 1

11 where a wavy line represents a bond in the up or in the down configuration,
 12 a dashed arrow represents a bond in the down configuration,
 13 a solid arrow represents a bond in the up configuration,
 14 R_1 is H, methyl, or ethyl, fluoro-substituted methyl or fluoro-substituted
 15 ethyl;

1 R_2 is *normal* alkyl of 1 to 4 carbons, fluoro-substituted *normal* alkyl of 1 to
 2 4 carbons, CH_2OCH_3 , $CH_2-O-CH_2-CH_3$, $CH_2-O-CH_2-OCH_3$, $CH_2-CH_2-O-CH_3$,
 3 CH_2SCH_3 , $CH_2-S-CH_2-CH_3$, $CH_2-S-CH_2-OCH_3$, $CH_2-CH_2-S-CH_3$, CH_2-S-CH_2-S-
 4 CH_3 , $CH_2-O-CH_2-S-CH_3$, CH_2NHCH_3 , $CH_2-NH-CH_2-CH_3$, $CH_2-NH-CH_2-OCH_3$,
 5 $CH_2-CH_2-NH-CH_3$, $CH_2-O-CH_2-NHCH_3$;

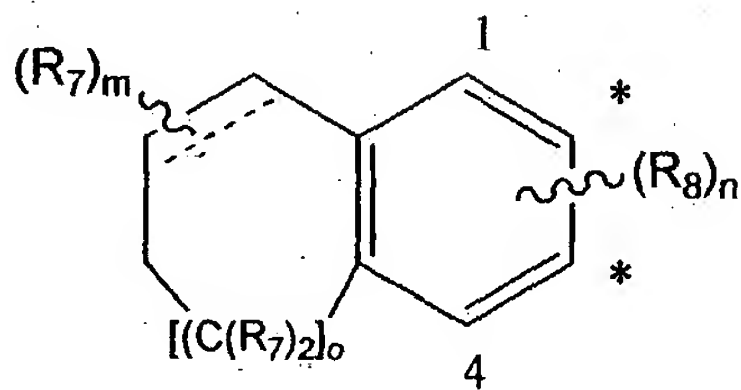
6 R_3 is H or F;

7 R_4 is H, alkyl of 1 to 3 carbons;

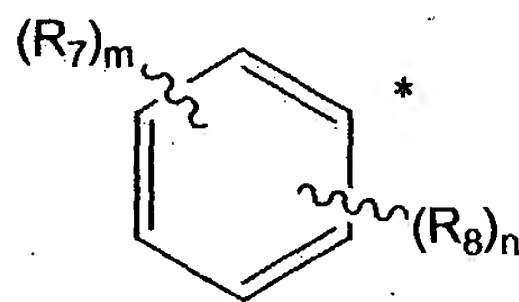
8 R_5 is H, alkyl of 1 to 6 carbons, OCH_2OR_6 or OCH_2OCOR_6 where R_6 is
 9 alkyl of 1 to 3 carbons, and

10 R is selected from the groups consisting of the radicals defined by **formulas**

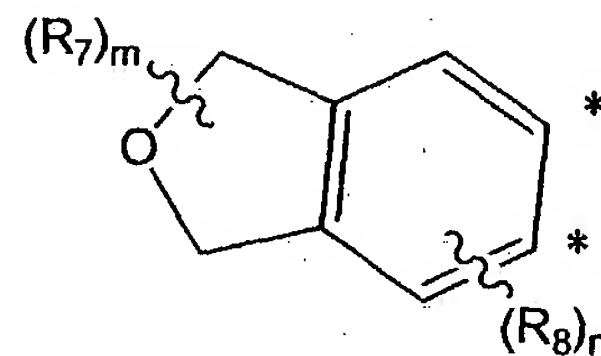
11 **(a) through (f)**



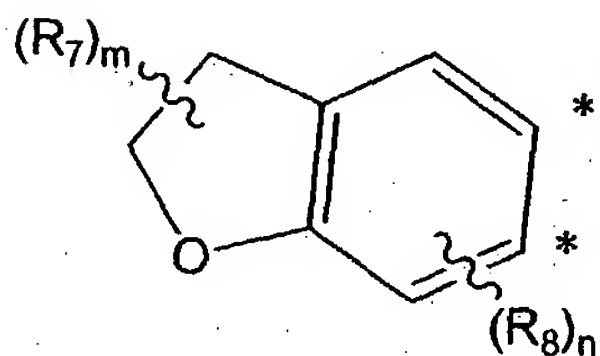
Formula (a)



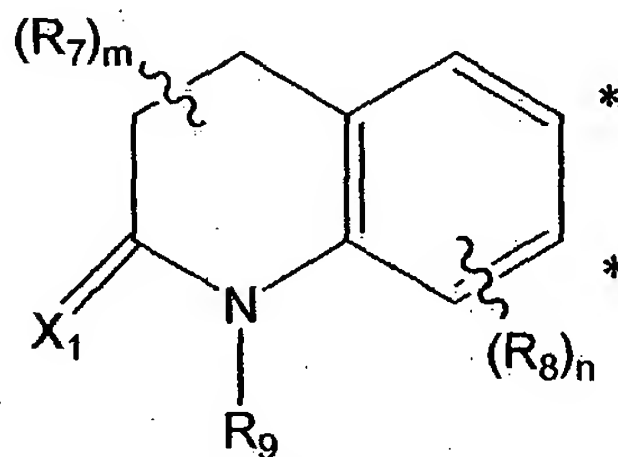
Formula (b)



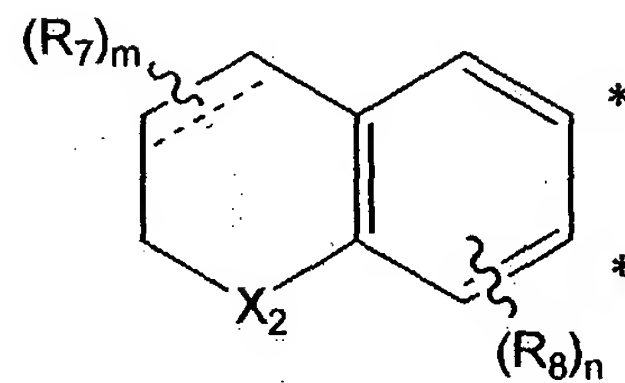
Formula (c)



Formula (d)



Formula (e)



Formula (f)

12 where the dashed line in a ring represents a bond, or absence of a bond,
 13

a * denotes a ring carbon to which the pentadienoyl-cyclopropyl group is attached, with the proviso that the pentadienoyl-cyclopropyl group is attached to only one carbon on the ring;

X_1 is O or S attached to the adjacent carbon with a double bond, or X_1 represents two hydrogens or R_7 groups attached to the adjacent carbon;

X_2 is O or S;

m is an integer having the values 0 to 6;

n is an integer having the values 0 to 3;

o is an integer having the values 0 or 1;

R_7 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br or I;

R_8 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, OC_{1-6} alkyl or SC_{1-6} alkyl,

R_9 is H or alkyl of 1 to 6 carbons, or a pharmaceutically acceptable salt of said compound.

The present invention also relates to pharmaceutical compositions incorporating the compounds of **Formula 1** and to methods of treatment of diabetic mammals with pharmaceutical compositions containing one or more compounds of **Formula 1** to reduce serum glucose levels in said mammals.

The present invention also relates to the methods of using the compounds of the invention to treat diseases and conditions which are responsive to treatment by retinoids.

DETAILED DESCRIPTION OF THE INVENTION

GENERAL EMBODIMENTS AND SYNTHETIC METHODOLOGY

1 Definitions

2 The term alkyl refers to and covers any and all groups which are known as
3 normal alkyl and branched-chain alkyl.

4 A pharmaceutically acceptable salt may be prepared for any compound in
5 this invention having a functionality capable of forming a salt, for example an acid
6 functionality. A pharmaceutically acceptable salt is any salt that retains the
7 activity of the parent compound and does not impart any deleterious or untoward
8 effect on the subject to which it is administered and in the context in which it is
9 administered.

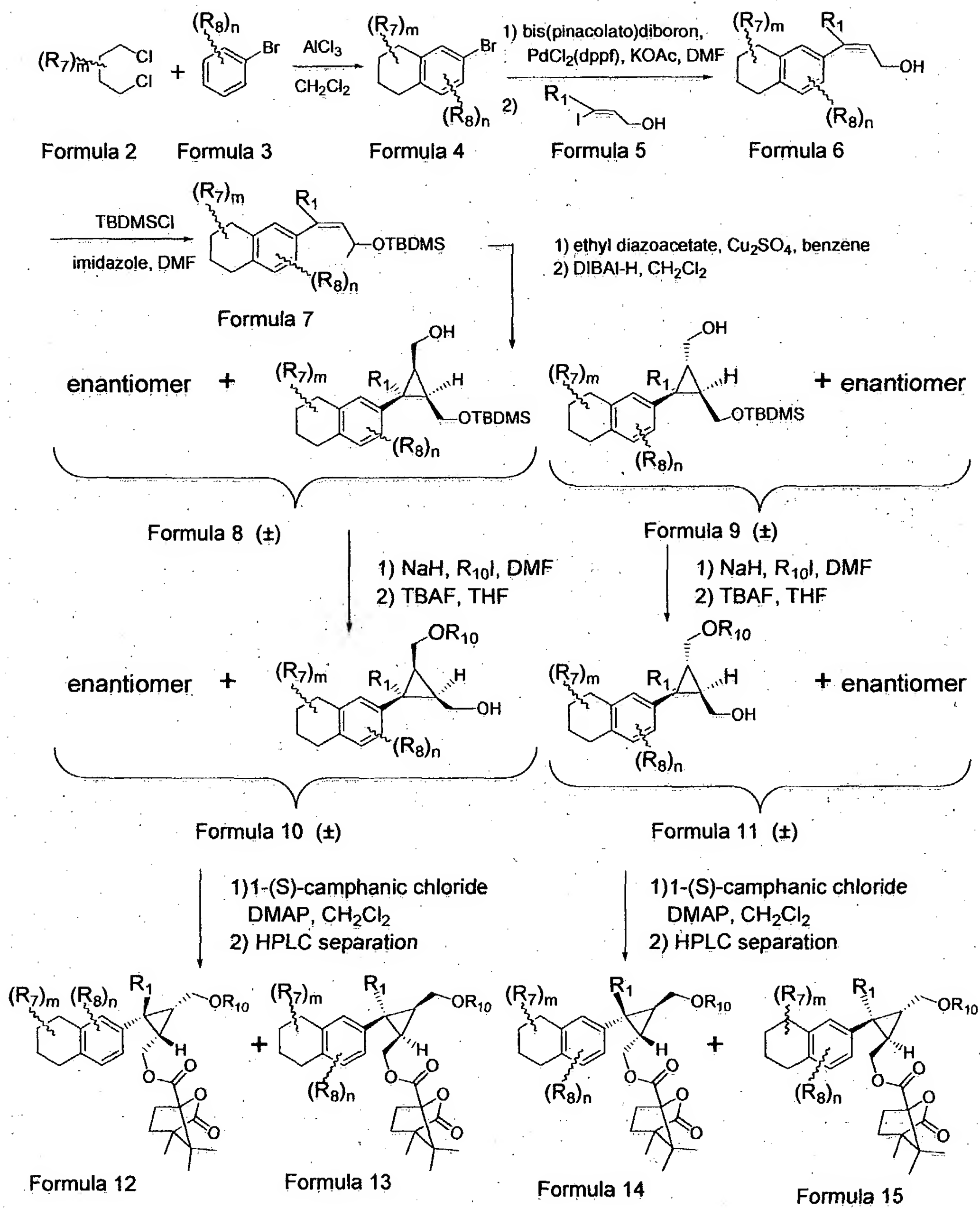
10 Pharmaceutically acceptable salts may be derived from organic or inorganic
11 bases. The salt may be a mono or polyvalent ion. Of particular interest are the
12 inorganic ions, sodium, potassium, calcium, and magnesium. Organic salts may be
13 made with amines, particularly ammonium salts such as mono-, di- and trialkyl
14 amines or ethanol amines. Salts may also be formed with caffeine, tromethamine
15 and similar molecules.

16 The compounds of the present invention include olefinic double bonds
17 about which *trans* and *cis* (**E** and **Z**) stereoisomerism can exist. The compounds of
18 the present invention have the specific orientations of substituents relative to the
19 double bonds as is indicated in the name of the respective compound, and/or by
20 specific showing in the structural formula of the orientation of the substituents
21 relative to the respective double bonds.

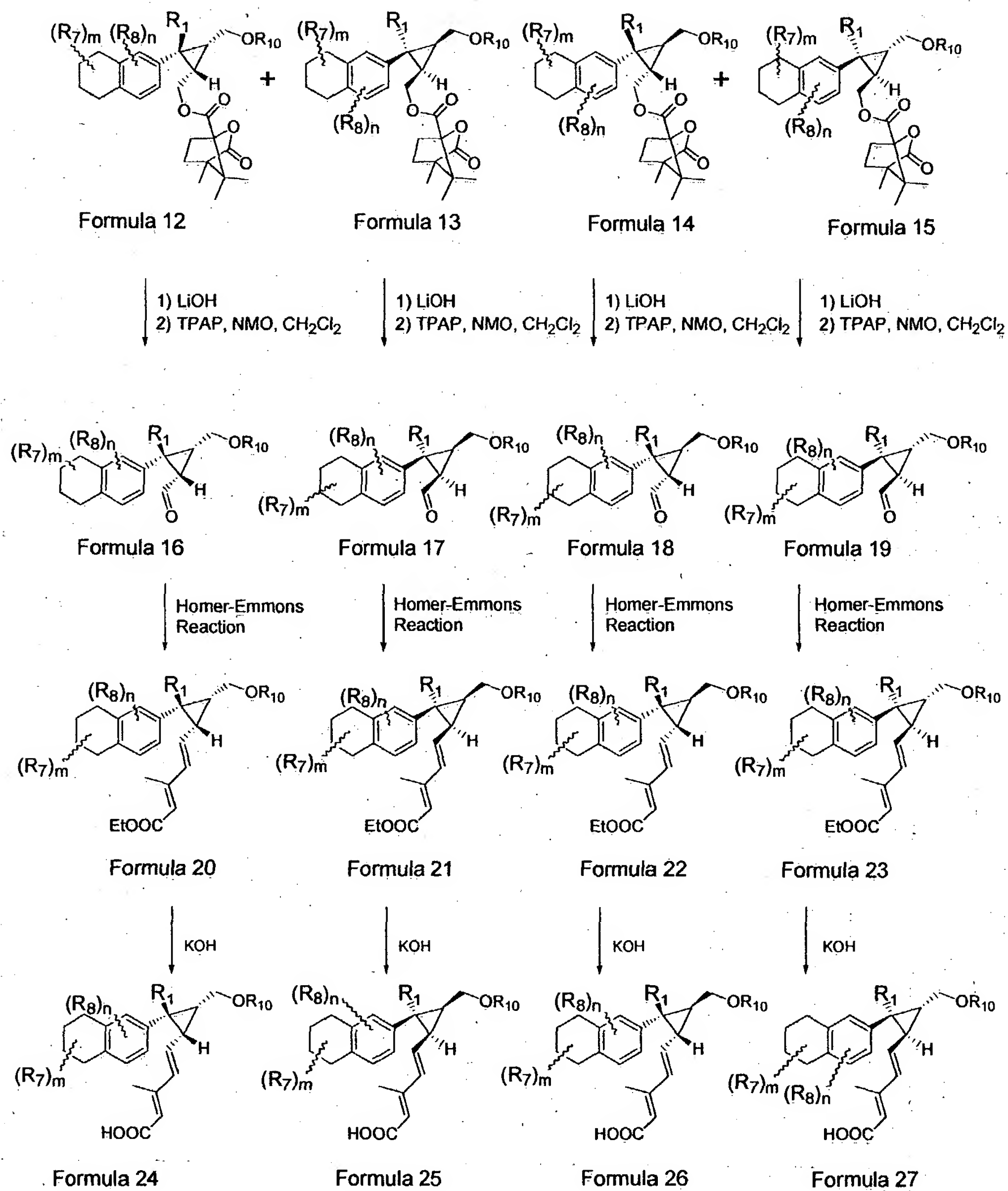
22 The compounds of the present invention also contain three or more chiral
23 centers and therefore may exist in enantiomeric and diastereomeric forms.

1 With respect to carbons 1 and 2 of the cyclopropyl ring (numbering shown
2 in **Formula 1**) all compounds of the invention have the orientation of substituents
3 shown in **Formula 1**. With regard to other chiral centers in the compounds, the
4 scope of the invention is intended to cover all possible orientations of the
5 substituents, thus including pure enantiomers (optical isomers), diastereomers,
6 mixtures of diastereomers and racemic mixtures of enantiomers.

7 **Reaction Scheme 1** discloses a presently preferred general synthetic route to
8 compounds of the invention where the variable **R** is a tetrahydronaphthalene
9 derivative in accordance with **Formula (a)** and where the tetrahydronaphthalene is
10 connected with its 2-position to the pentadienoyl-cyclopropyl group.



Reaction Scheme 1



Reaction Scheme 1 continued

1 Although **Reaction Scheme 1** is general, for the sake of easier exemplification and
2 illustration the variable **R₃** of **Formula 1** is H in this scheme, the variable **R₄** is
3 methyl and the variable **R₂** is CH₂OR₁₀, as in the preferred examples. Based on the
4 present disclosure those skilled in the art would be able to employ state-of-the-art
5 reactions to obtain compounds of the invention where **R₃**, **R₄** and **R₂** have the
6 scopes defined in **Formula 1**.

7 Referring now to **Reaction Scheme 1**, one starting material is a dichloro
8 substituted alkane compound of **Formula 2** that already has the **R₇** substituent or
9 substituents. Another starting material is a bromobenzene derivative of **Formula 3**
10 that already has the **R₈** substituent. The substituted dichloro alkanes of **Formula**
11 **2** and the substituted bromobenzenes of **Formula 3** are either available
12 commercially, or can be prepared in accordance with the chemical scientific and
13 patent literature, or by such modifications of known synthetic procedures that are
14 readily apparent to those skilled in the art. An example for the dichloro alkane
15 derivative of **Formula 2** that is utilized for the synthesis of several preferred
16 compounds of the invention is 2,5-dichloro-2,5-dimethylhexane. Bromobenzene is
17 used for the synthesis of several preferred compounds and serves as an example for
18 the compounds of **Formula 3**. The compounds of **Formula 2** and of **Formula 3**
19 are reacted under *Friedel Crafts* conditions to provide a substituted bromo-
20 tetrahydronaphthalene derivative of **Formula 4**. The substituted bromo-
21 tetrahydronaphthalene derivative of **Formula 4** is reacted with a 3-iodo-alk-2Z-en-
22 1-ol of **Formula 5** in the presence of bis(pinacolato)diboron, potassium acetate
23 and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium (PdCl₂(dppf)₂) in

1 dimethylformamide (DMF) to give a 3-(5,6,7,8-tetrahydro-naphthalen-2-yl)-alk-
2 2Z-en-1-ol compound of **Formula 6**. In **Formula 5** R_1 is defined as in connection
3 with **Formula 1**. An example for the reagent of **Formula 5** that is utilized for the
4 synthesis of several preferred compounds of the invention is 3-iodo-but-2Z-en-1-ol
5 that can be obtained in accordance with the disclosure of United States Patent No.
6 6,147,224, incorporated herein by reference.

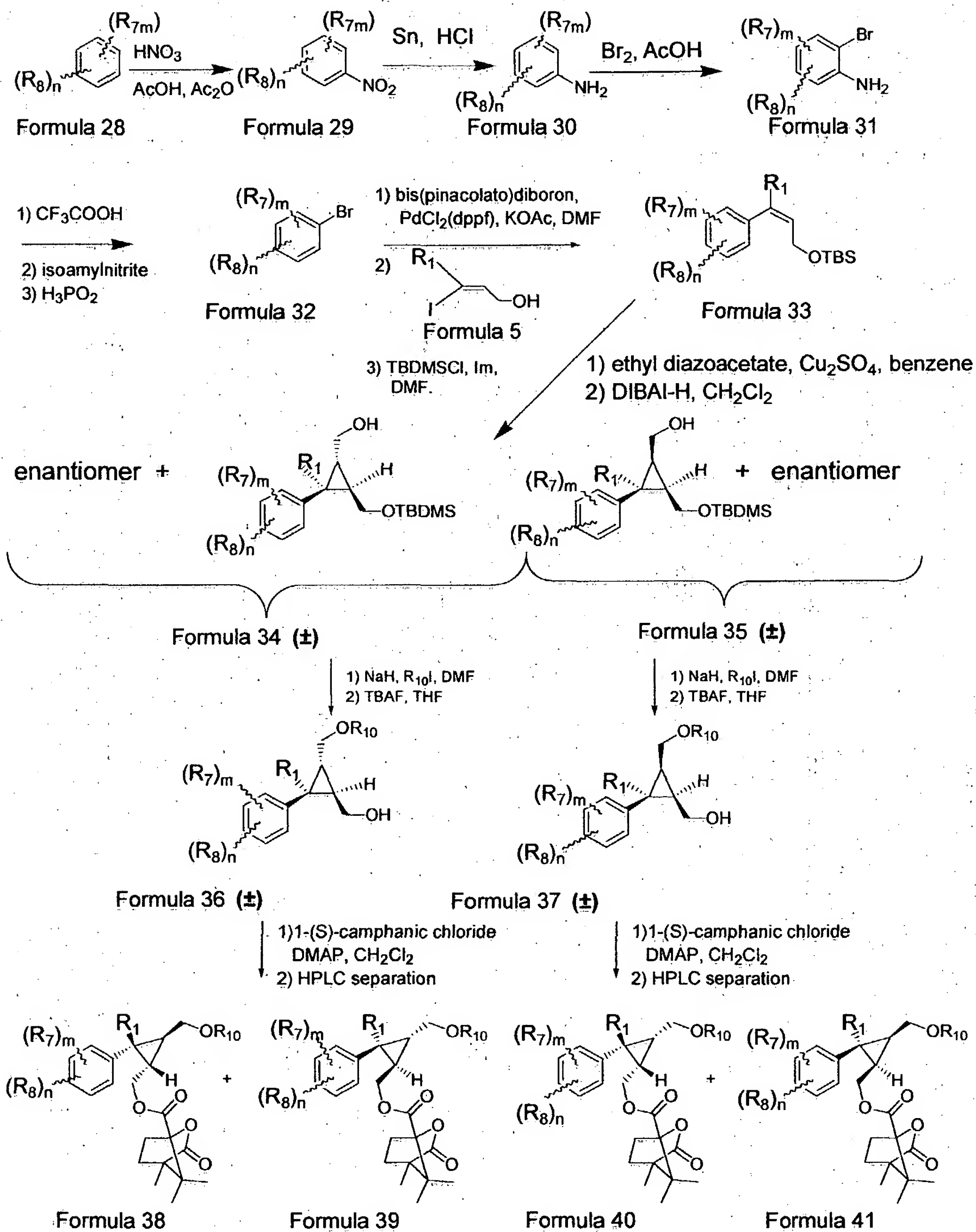
7 The free hydroxyl group of the compound of **Formula 6** is protected by
8 treatment with *tert*-butyldimethylsilyl chloride (TBDMSCl) in the presence of
9 imidazol, to give the *tert*-butyldimethyl-[3-(5,6,7,8-tetrahydronaphthalen-2-yl)-alk-
10 2Z-enyloxy]silane compound of **Formula 7**. The compound of **Formula 7** is then
11 reacted with ethyl diazoacetate in an inert solvent, such as benzene, in the presence
12 of anhydrous copper (II) sulfate, and the resulting carboxylic acid ester derivative
13 is reduced to the primary alcohol level by treatment with di-*iso*-butyl aluminum
14 hydride (DIBAL-H). A pair of diastereomeric cyclopropyl derivatives are the result
15 of the latter reaction, with each diastereomer of the pair being present in a
16 substantially racemic form, formed of two enantiomers. The diastereomers are
17 shown as **Formula 8** and **Formula 9**, respectively. It can be seen that the
18 difference between the two diastereomers is in the configuration of the C-3 carbon
19 of the cyclopropyl ring. Each of the diastereomers of **Formula 8** and of **Formula**
20 **9**, respectively, is reacted with an alkylating agent of the formula $R_{10}I$ in the
21 presence of strong base, such as sodium hydride, to introduce the R_{10} group into
22 the free primary hydroxyl function of the molecule. Thereafter the *tert*-
23 butyldimethylsilyl protecting group is removed by treatment with tetrabutyl -

1 ammonium fluoride (TBAF). The variable R_{10} is defined in this connection as a
2 radical that together with the CH_2O group already attached to the C-3 carbon of the
3 cyclopropyl ring would provide the R_2 radical defined in connection with **Formula**
4 **1**. Preferred examples for the reagent $R_{10}I$ are methyl or ethyl iodide. Instead of
5 an iodo containing alkylating group other alkylating agents could also be used, and
6 may become readily apparent to those skilled in the art in light of the present
7 disclosure. The products of the alkylations and removal of the *tert*-
8 butyldimethylsilyl protecting group are the diastereomeric racemates 3-
9 alkoxymethyl-2-alkyl-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl-
10 methanols of **Formulas 10** and **11**, respectively.

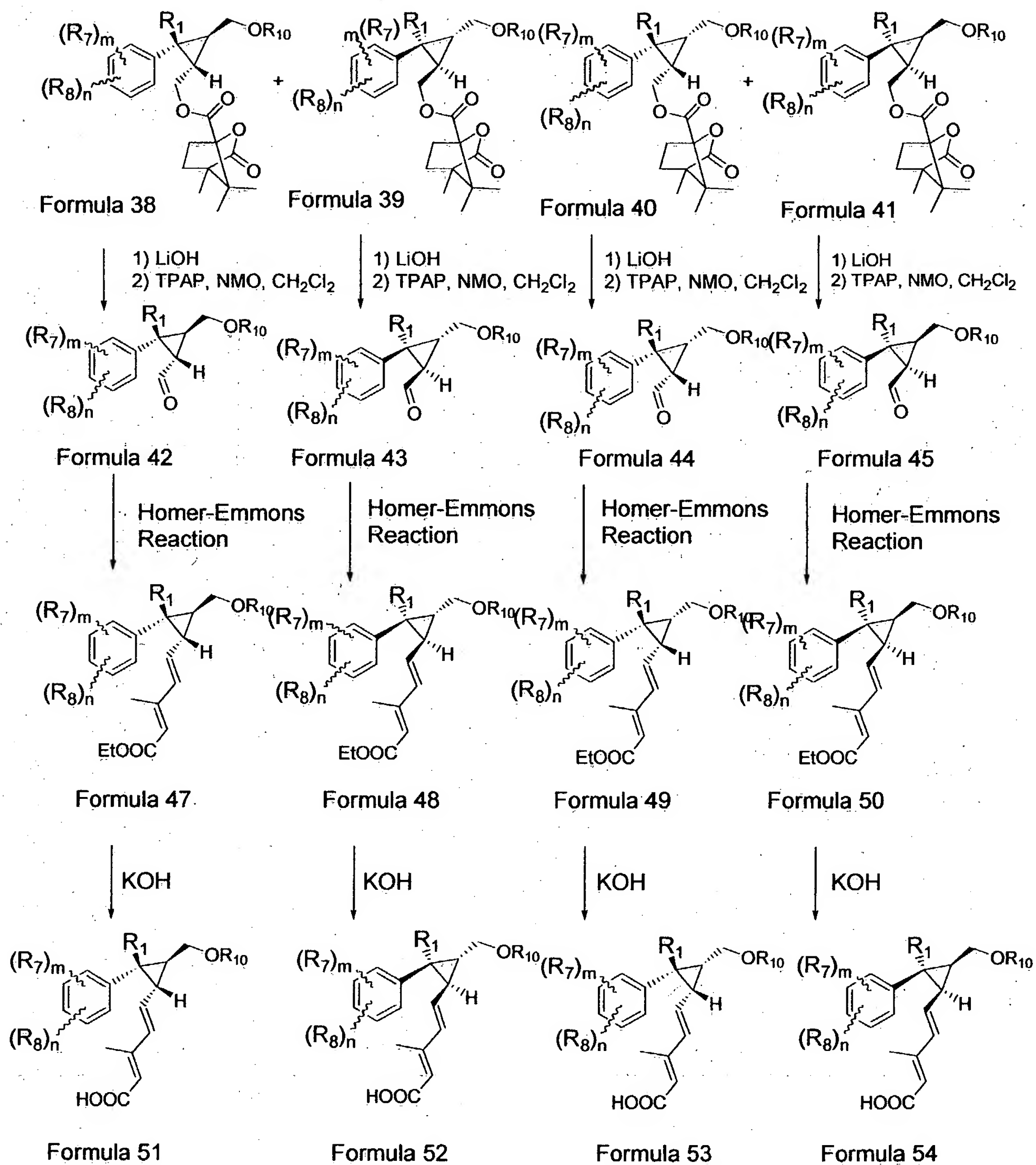
11 The two diastereomers of **Formulas 10** and **11**, respectively are resolved
12 into the corresponding pure enantiomers by treatment with 1-(S)-(-)-camphanic
13 chloride and *N,N*-dimethylaminopyridine (DMAP) followed by high pressure
14 liquid chromatography (HPLC) separation, of the resulting 1-(S)-(-)-camphanic
15 esters of **Formulas 12, 13** and of **Formulas 14** and **15**, respectively. After
16 separation, each of the four compounds is saponified to remove the 1-(S)-(-)-
17 camphanoyl group and the resulting primary alcohols are oxidized to the aldehyde
18 level by treatment with tetrapropylammonium perruthenate (TPAP) in the presence
19 of added molecular sieves and 4-methylmorpholine *N*-oxide (NMO). The resulting
20 aldehydes are shown as compounds of **Formulas 16, 17, 18** and **19**. Each of the
21 aldehydes is subjected to a *Horner Emmons* reaction with the reagent
22 triethylphosphono-3-methyl-2*E*-butenoate (available from Aldrich) in the presence
23 of strong base, such as *n*-butyl lithium and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-

1 pyrimidinone (DMPU) in an aprotic solvent such as tetrahydrofuran (THF), to give
2 the corresponding ethyl 5-[3-alkoxymethyl-2-alkyl-2-(-5,6,7,8-tetrahydro-
3 naphthalen-2-yl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoates of **Formulas 20**,
4 **21**, **22** and **23**. The compounds of **Formulas 21** and **23** have the configuration at
5 the C-1 and C-2 carbons of the cyclopropyl ring as shown in **Formula 1**, and are
6 within the scope of the invention. These ester compounds are saponified by
7 treatment with base, such as potassium hydroxide, to provide the free carboxylic
8 acids or their salts, of the **Formulas 24**, **25**, **26** and **27**. The compounds of
9 **Formulas 25** and **27** have the configuration at the C-1 and C-2 carbons of the
10 cyclopropyl ring as shown in **Formula 1**, and are within the scope of the invention.

11 **Reaction Scheme 2** discloses a general synthetic route to compounds of the
12 invention where the **R** group of **Formula 1** is phenyl, as shown by **Formula (b)**.
13 Again, although **Reaction Scheme 2** is general, for the sake of easier
14 exemplification and illustration the variable **R₃** of **Formula 1** is H in this scheme,
15 the variable **R₄** is methyl and the variable **R₂** is CH₂OR₁₀, as in the preferred
16 examples. Based on the present disclosure those skilled in the art would be able to
17 employ state-of-the-art reactions to obtain compounds of the invention where the
18 **R₂**, **R₃** and **R₄** groups have the scopes defined in **Formula 1**.



Reaction Scheme 2



Reaction Scheme 2 continued

1 Referring now to **Reaction Scheme 2**, one starting material is a phenyl
2 compound of **Formula 28** that already has the **R₇** and **R₈** substituents. The
3 substituted phenyl compounds of **Formula 28** are either available commercially,
4 or can be prepared in accordance with the chemical scientific and patent literature,
5 or by such modifications of known synthetic procedures that are readily apparent
6 to those skilled in the art. An example for the phenyl compound of **Formula 28**
7 that is utilized for the synthesis of several preferred compounds of the invention is
8 1,3-di-*iso*-propylbenzene (available from Aldrich). A nitro group is introduced
9 into the phenyl compound of **Formula 28** by treatment with nitric acid in acetic
10 acid and acetic anhydride and the resulting nitrophenyl compound of **Formula 29**
11 is reduced by treatment with mossey tin and hydrochloric acid to provide a
12 substituted aniline compound of **Formula 30**. The substituted aniline compound
13 of **Formula 30** is brominated in acetic acid to provide the substituted bromo-
14 aniline of **Formula 31**. The substituted bromo-aniline of **Formula 31** is converted
15 into a bromo-phenyl compound of **Formula 32**. Those skilled in the art will
16 recognize that depending on the nature of the substituents **R₇** and **R₈**, other
17 synthetic routes may be available to obtain the bromo compound of **Formula 32**,
18 or the bromo-phenyl compound of **Formula 32** may be available commercially.

19 The bromo-phenyl compound of **Formula 32** is then reacted with a 3-iodo-
20 alk-2*Z*-en-1-ol of **Formula 5** in the presence of bis(pinacolato)diboron, potassium
21 acetate and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium
22 (PdCl₂(dppf)₂) in dimethylformamide (DMF) to give a phenyl-alk-2*Z*-en-1-ol
23 compound, the free hydroxyl group of which is protected by treatment with *tert*-

1 butyldimethylsilyl chloride (TBDMSCl) in the presence of imidazol, to give the
2 *tert*-butyldimethyl-[(phenyl)-alk-2Z-enyloxy]silane compound of **Formula 33**. An
3 example for the reagent of **Formula 5** that is utilized for the synthesis of several
4 preferred compounds of the invention in the series where the **R** variable of
5 **Formula 1** is phenyl, is 3-iodo-but-2Z-en-1-ol.

6 The compound of **Formula 33** is then reacted with ethyl diazoacetate in an
7 inert solvent, such as benzene, in the presence of anhydrous copper (II) sulfate,
8 and the resulting carboxylic acid ester derivative is reduced to the primary alcohol
9 level by treatment with di-*iso*-butyl aluminum hydride (DIBAL-H). A pair of
10 diastereomeric cyclopropyl derivatives are the result of the latter reaction, with
11 each diastereomer of the pair being present in a substantially racemic form, formed
12 of two enantiomers. The diastereomers are shown by **Formula 34** and **Formula**
13 **35**, respectively. It can be seen that the difference between the two diastereomers
14 is in the configuration of the C-3 carbon of the cyclopropyl ring.

15 Each of the diastereomers of **Formula 34** and of **Formula 35**, respectively,
16 is reacted with an alkylating agent of the formula $R_{10}I$ in the presence of strong
17 base, such as sodium hydride, to introduce the R_{10} group into the free primary
18 hydroxyl function of the molecule. Thereafter the *tert*-butyldimethylsilyl
19 protecting group is removed by treatment with tetrabutyl ammonium fluoride
20 (TBAF). The variable R_{10} is defined as in connection with **Reaction Scheme 1**.
21 In this sequence of reaction also, the preferred examples for the reagent $R_{10}I$ are
22 methyl or ethyl iodide. The products of the alkylations and removal of the *tert*-
23 butyldimethylsilyl protecting group are the diastereomeric racemates 3-

1 alkoxymethyl-2-alkyl-(phenyl)-cyclopropyl-methanols of **Formulas 36 and 37**,
2 respectively.

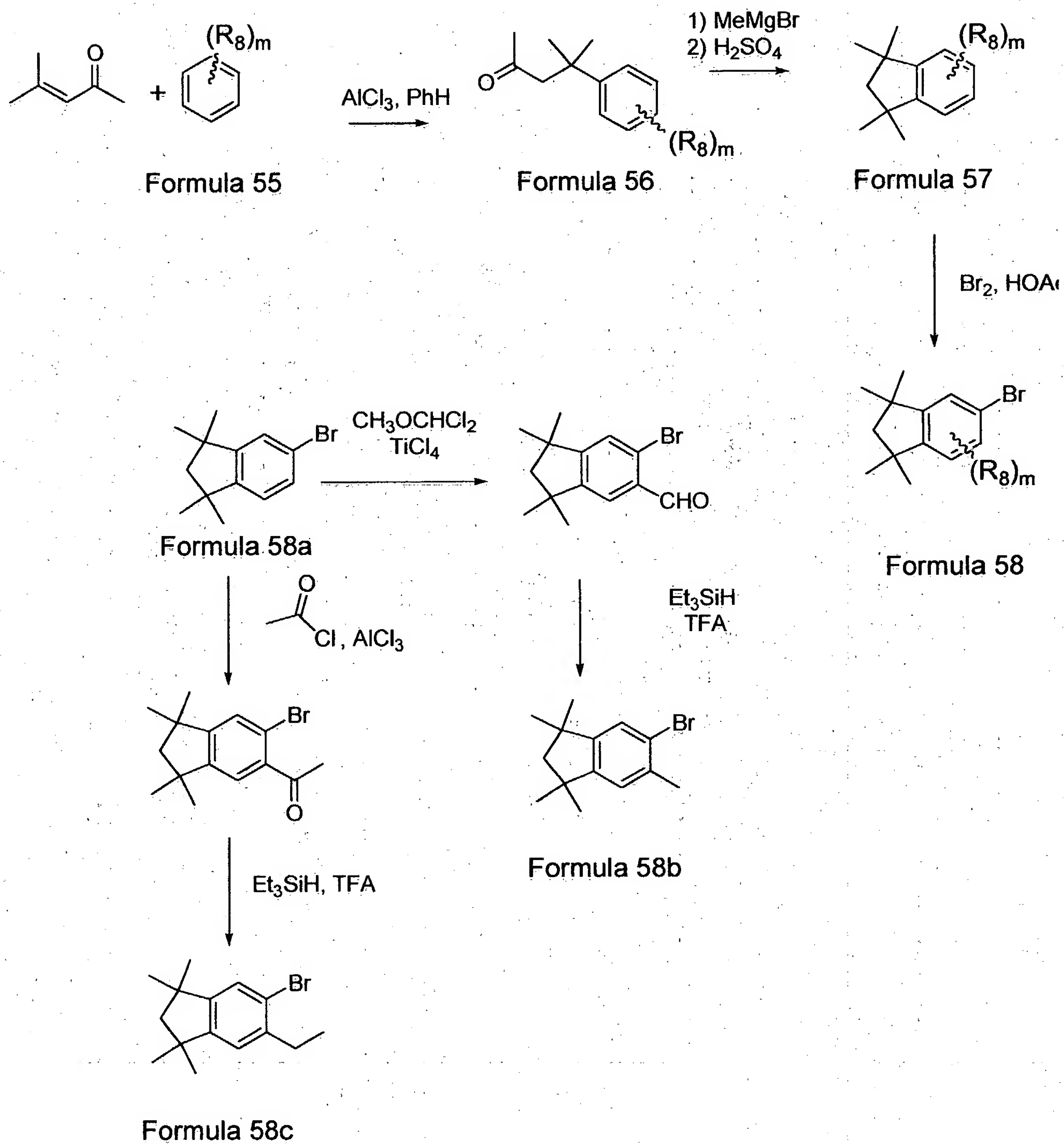
3 The two diastereomers of **Formulas 36 and 37**, respectively, are resolved
4 into the corresponding pure enantiomers, and the resolved primary alcohols are
5 subjected to substantially the same sequence of reactions as shown and described
6 in connection with **Reaction Scheme 1**, to give the ethyl [3-alkoxymethyl-2-
7 methyl-2-(phenyl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoates of **Formulas 47**,
8 **48, 49 and 50**. The compounds of **Formulas 48 and 50** have the configuration at
9 the C-1 and C-2 carbons of the cyclopropyl ring as shown in **Formula 1**, and are
10 within the scope of the invention. These ester compounds are saponified by
11 treatment with base, such as potassium hydroxide, to provide the free carboxylic
12 acids or their salts, of the **Formulas 51, 52, 53 and 54**. The compounds of
13 **Formulas 52 and 54** have the configuration at the C-1 and C-2 carbons of the
14 cyclopropyl ring as shown in **Formula 1**, and are within the scope of the invention.

15 Generally speaking, compounds of the invention where the variable **R** of
16 **Formula 1** is other than the examples specifically shown in **Reaction Schemes 1**
17 and **2** can be made by subjecting bromo-compounds analogous to the bromo
18 compounds of **Formulas 4 and 32** to the same sequence of reactions to which the
19 bromo compounds of **Formulas 4 and 32**, are subjected to in **Reaction Schemes 1**
20 and **2**, respectively. These bromo compounds can generally speaking be obtained
21 in accordance with the chemical literature of by such modifications of known
22 synthetic procedures which will become readily apparent to those skilled in the art

1 in light of the present disclosure. **Reaction Schemes 3 to 9** serve as examples how
2 to obtain these bromo compounds.

3 **Reaction Scheme 3** discloses a synthetic route to compounds of the
4 invention which are indan derivatives, that is where the variable **o** of **Formula (a)**
5 is zero and where the dashed line of **formula (a)** represents absence of a bond. For
6 the sake of simplicity of illustration the scheme illustrates the synthesis of the
7 compounds of the invention where the variable $(R_7)_m$ represent geminal dimethyl
8 groups substituting carbons 5 and 7 of the indan nucleus. Thus, in accordance with
9 this scheme 4-methyl-pent-3-en-2-one is reacted under *Friedel Crafts* conditions
10 with a benzene derivative of **Formula 55** to yield 4-phenyl-4,4-dimethyl-but-2-one
11 derivative of **Formula 56**. The variables R_8 and **m** are defined as in connection
12 with **Formula 1**. The 4-phenyl-4,4-dimethyl-but-2-one derivative of **Formula 56**
13 is then reacted with methylmagnesium bromide and thereafter cyclized by
14 treatment with acid to yield the indan derivative of **Formula 57**. The indane
15 derivative of **Formula 57** is brominated with bromine in acetic acid to provide the
16 bromo-indan derivative of **Formula 58**.

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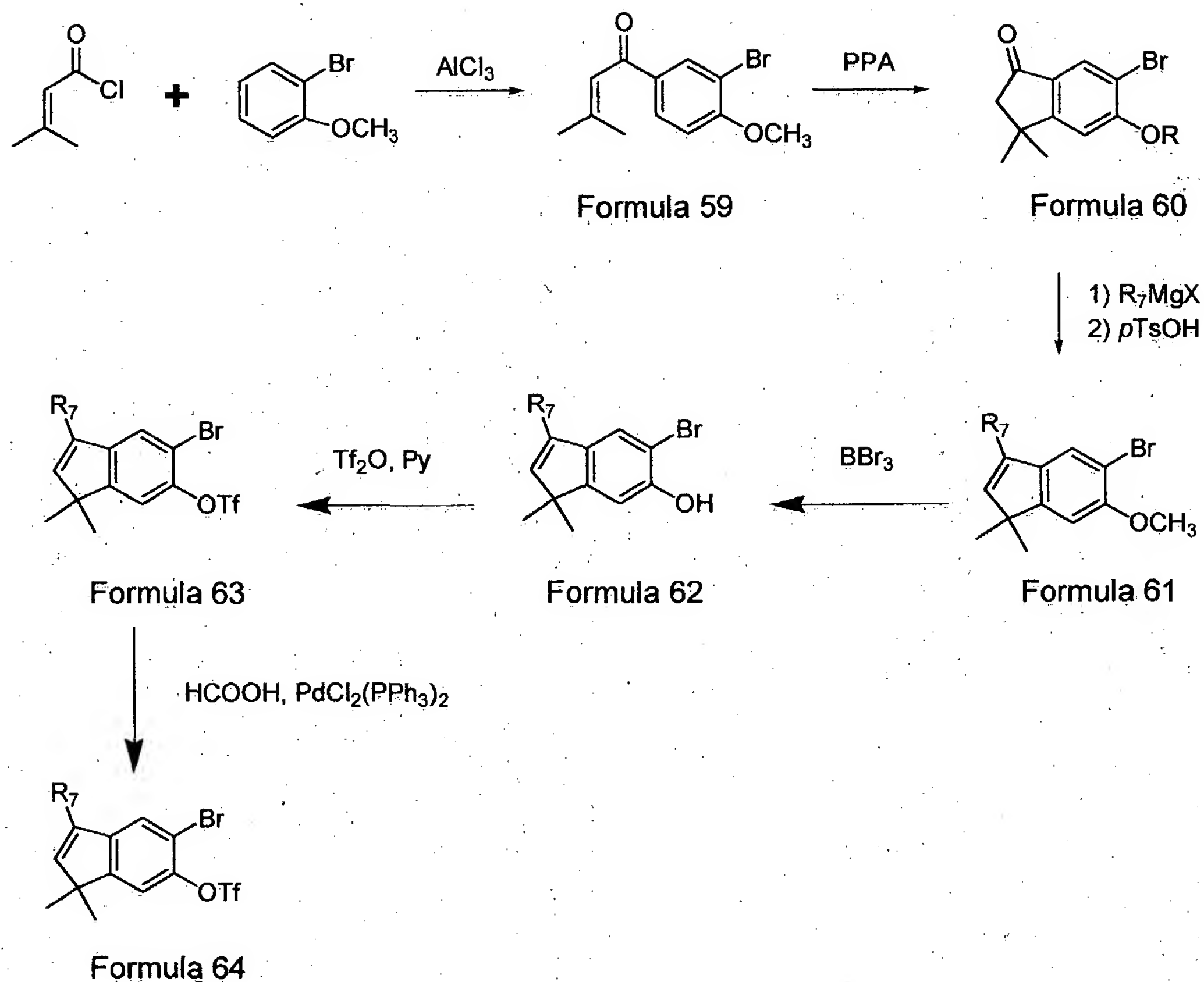
Reaction Scheme 3

1 The bromo-indan of **Formula 58** is thereafter subjected to the same
2 sequence of reactions (not shown in **Scheme 3**) as the bromo compounds of
3 **Formulas 4** and **32** of **Reaction Schemes 1** and **2**, respectively, to provide
4 compounds of the invention in accordance with **Formula 1** where the variable **R** is
5 an indan radical. **Reaction Scheme 3** also shows alternative routes whereby a
6 methyl or ethyl substituent corresponding to the variable **R₈** can be introduced into
7 the aromatic portion of the indan nucleus.

8 **Reaction Scheme 4** discloses a synthetic route to compounds of the
9 invention which are indene derivatives, that is where the variable **o** of **Formula (a)**
10 is zero and where the dashed line of **formula (a)** represents a bond. For the sake
11 of simplicity of illustration the scheme illustrates the synthesis of the compounds
12 of the invention where the variable **(R₇)_m** represent a geminal dimethyl groups
13 substituting carbons 5 of the indene nucleus. Thus, in accordance with this scheme
14 3-methyl-but-2-en-oyl chloride (available from Aldrich) is reacted with 2-
15 bromoanisole (available from Aldrich) under *Friedel Crafts* conditions to provide
16 an acylated bromoanisole derivative of **Formula 59**. The compound of **Formula**
17 **59** is then ring closed by treatment with polyphosphoric acid (PPA) to give the
18 bromo-indanone derivative of **Formula 60**. The bromo-indanone of **Formula 60**
19 is reacted with a Grignard reagent **R₇MgX** (where **R₇** is defined as in connection
20 with **Formula 1** and **X** is halogen) and the resulting tertiary alcohol (not shown) is
21 treated with acid such as *para*-toluenesulfonic acid (*pTsOH*) to provide the bromo
22 indene derivative of **Formula 61**. The methyl group of the methoxy group of the
23 compound of **Formula 61** is removed by treatment with boron tribromide to give

1 the hydroxy-bromoindene compound of **Formula 62**. The hydroxy-bromo-indene
2 of **Formula 62** is reacted with trifluoromethylsulfonic acid anhydride (Trf_2O) in
3 pyridine (Py) to give the corresponding trifluoromethylsulfonate (triflate) of
4 **Formula 63**. The triflate of **Formula 63** is then reacted with formic acid in the
5 presence of $\text{PdCl}_2(\text{PPh}_3)_2$ catalyst to give the bromoindene derivative of **Formula**
6 **64**. The compound of **Formula 64** is subjected to the same sequence of reactions
7 (not shown in **Scheme 4**) as the bromo compounds of **Formulas 4** and **32** of
8 **Reaction Schemes 1** and **2**, respectively, to provide compounds of the invention in
9 accordance with **Formula 1** where the variable **R** is an indene radical.

10

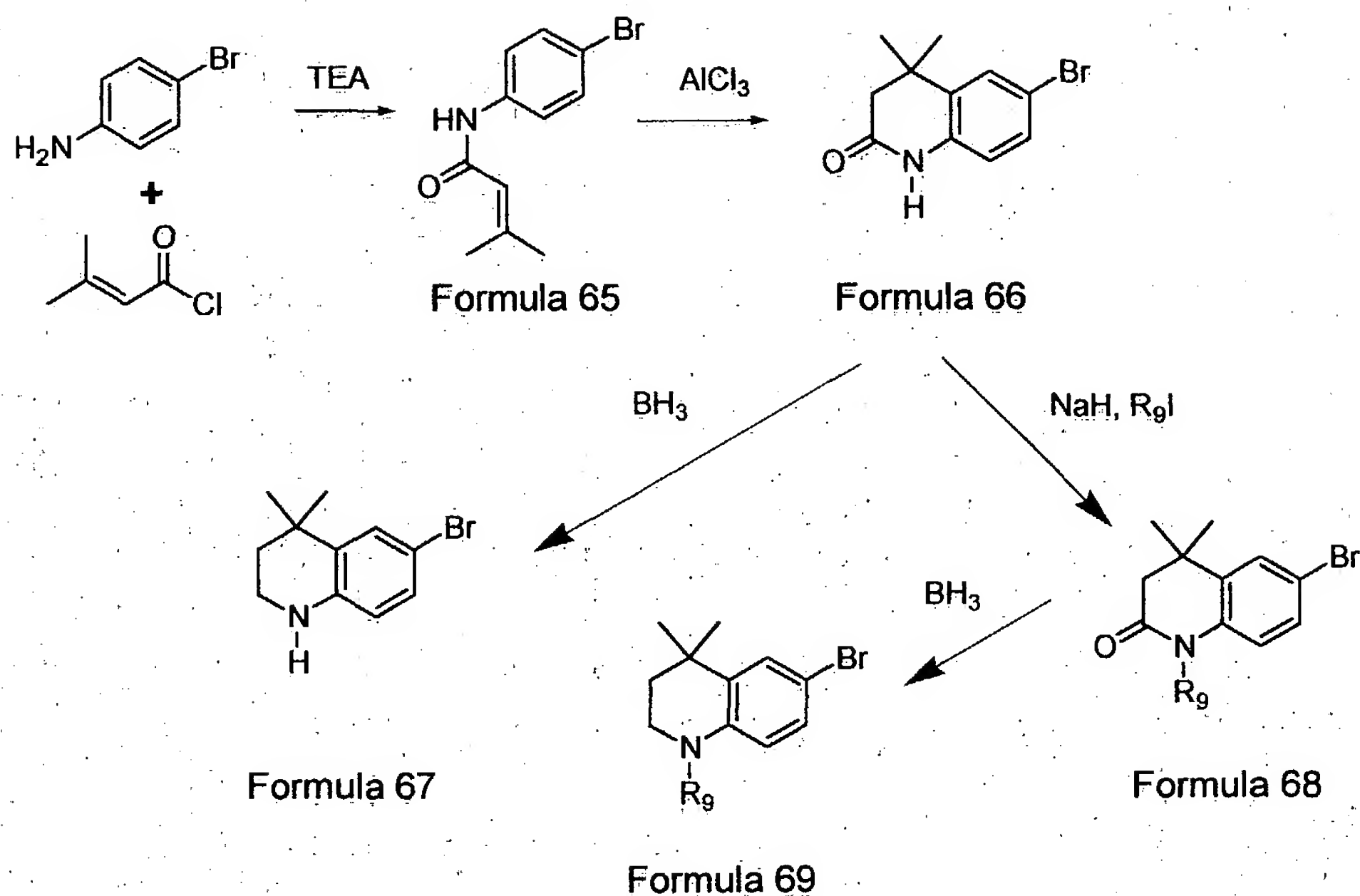


Reaction Scheme 4

Reaction Scheme 5 discloses a synthetic route to compounds of the invention which are tetrahydroquinoline or tetrahydroquinolinone derivatives, that is where the variable **R** of **Formula 1** is represented by **Formula (e)**. For the sake

1 of simplicity of illustration, the scheme illustrates the synthesis of the compounds
2 of the invention where the variable $(R_7)_m$ represents a geminal dimethyl groups
3 substituting carbon 4 of the tetrahydroquinoline nucleus. Thus, in accordance with
4 this scheme 4-bromoaniline is reacted with dimethyl-acryloyl chloride in the
5 presence of triethylamine (TEA) to give the corresponding amide compound of
6 **Formula 65**. The amide of **Formula 65** is ring closed under *Friedel Crafts*
7 conditions ($AlCl_3$) to give the 6-bromo-tetrahydroquinoline-2-one compound of
8 **Formula 66**. The 6-bromo-tetrahydroquinoline-2-one compound of **Formula 66**
9 is reacted with borane (BH_3) to remove the keto group and provide the 6-
10 bromoquinoline of **Formula 67**. Alternatively the 6-bromo-tetrahydroquinoline-2-
11 one compound of **Formula 66** alkylated on the nitrogen atom by treatment with an
12 alkylating agent, such as R_9I where R_9 is an alkyl group of 1 to 6 carbons, to give
13 the compound of **Formula 68**. The keto function of the *N*-alkylated 6-bromo-
14 tetrahydroquinoline-2-one compound of **Formula 68** can also be removed by
15 treatment with borane (BH_3) to provide *N*-alkylated 6-bromoquinoline compounds
16 of **Formula 69**. The bromo compounds of Formulas **66**, **67**, **68** and **69** are
17 subjected to the same sequence of reactions (not shown in **Scheme 5**) as the bromo
18 compounds of **Formulas 4** and **32** of **Reaction Schemes 1** and **2**, respectively, to
19 provide compounds of the invention in accordance with **Formula 1** where the
20 variable **R** is a tetrahydroquinoline or tetrahydroquinolin-2-one radical.

21

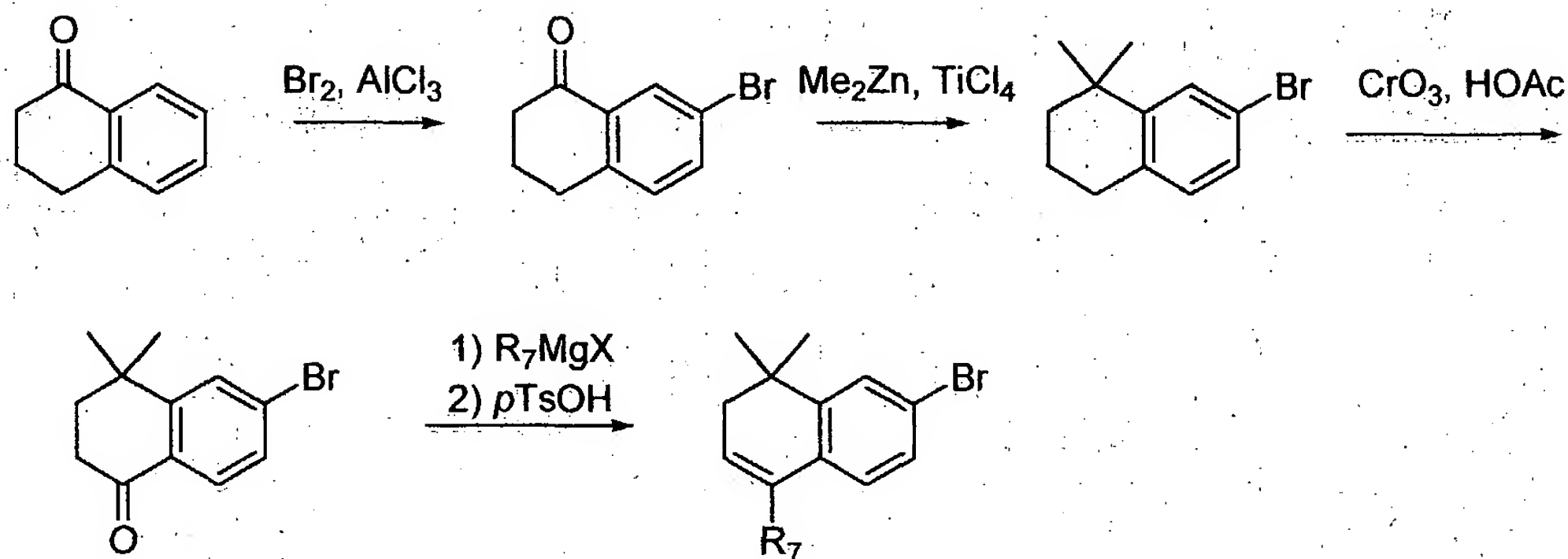


Reaction Scheme 5

Reaction Scheme 6 discloses a synthetic route to compounds of the invention which are dihydronaphthalene derivatives, that is where the variable **R** of **Formula 1** is represented by **Formula (a)** where the dashed line represents a bond and where the variable **o** represents the integer one (1). For the sake of simplicity of illustration the scheme illustrates the synthesis of the compounds of the invention where the variable $(\text{R}_7)_m$ represents geminal dimethyl groups substituting a carbon of the non-aromatic portion of the dihydronaphthalene nucleus. Thus, in accordance with this scheme, tetrahydronaphthalene-1-one (available from Aldrich) is brominated to provide 3-bromo-tetrahydronaphthalene-1-one. The keto function of 3-bromo-tetrahydronaphthalene-1-one is converted by treatment with

dimethylzinc and titanium tetrachloride to geminal dimethyl groups, to give 1-bromo-3,3-dimethyl tetrahydronaphthalene. 1-Bromo-3,3-dimethyl tetrahydronaphthalene is oxidized by treatment with chromium trioxide in acetic acid to give 1-bromo-3,3-dimethyl-tetrahydronaphthalene-6-one. 1-Bromo-3,3-dimethyl-tetrahydronaphthalene-6-one is then reacted with a Grignard reagent of the formula R_7MgX (where R_7 is defined as in connection with **Formula 1** and **X** is halogen) to give the bromo-dihydronaphthalene derivative of **Formula 70**.

The bromo compound of **Formula 70** is subjected to the same sequence of reactions (not shown in **Scheme 6**) as the bromo compounds of **Formulas 4** and **32** of **Reaction Schemes 1** and **2**, respectively, to provide compounds of the invention in accordance with **Formula 1** where the variable **R** is a dihydronaphthalene radical.

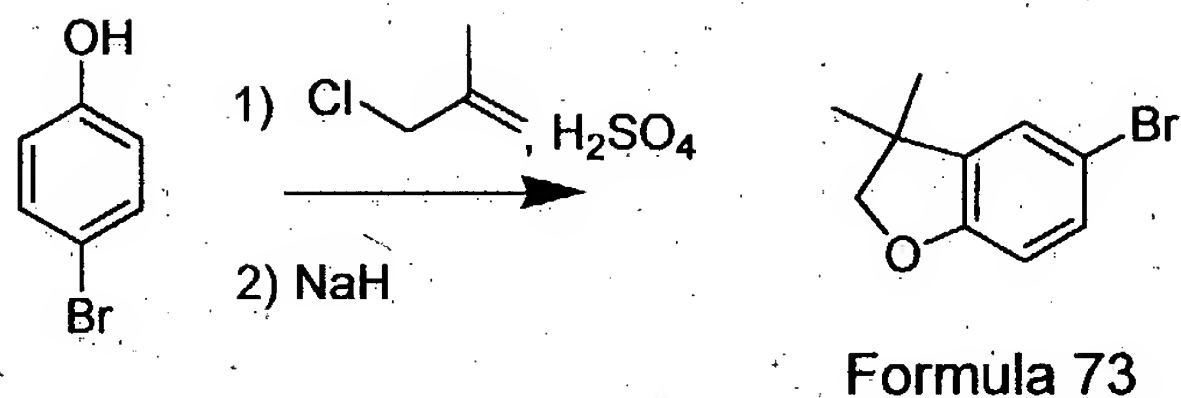
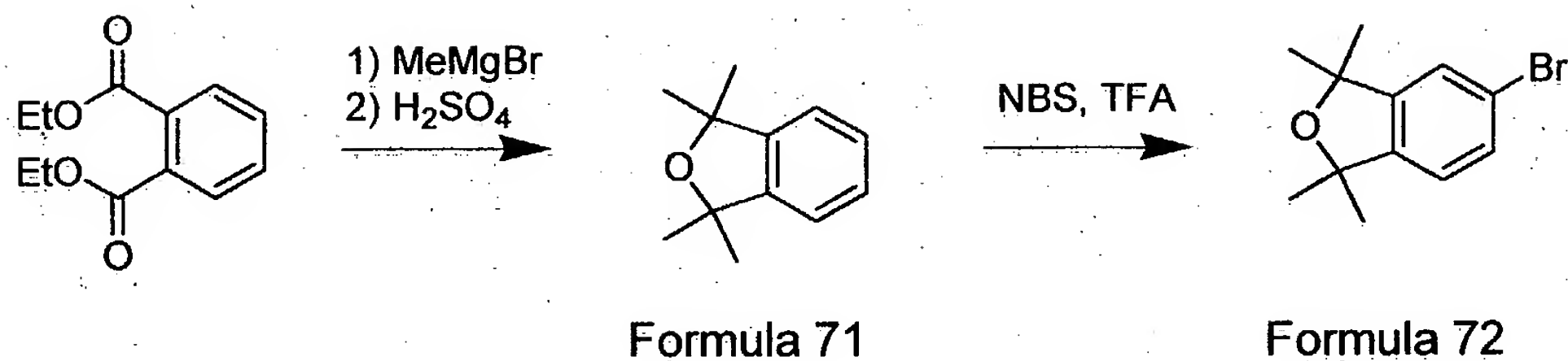


Formula 70

Reaction Scheme 6

1 **Reaction Scheme 7** serves as an example for preparing compounds of the
2 invention which are benzodihydrofuran derivatives, that is where the variable **R** of
3 **Formula 1** is represented by **Formula (c)** or **Formula (d)**. For the sake of
4 simplicity of illustration the scheme illustrates the synthesis of the compounds of
5 the invention where the variable (**R**₇)_m represents geminal dimethyl groups
6 substituting one or two carbons of the non-aromatic portion of the
7 dihydrobenzofuran nucleus. Thus, in accordance with this scheme phthalic acid
8 diethylester (available from Aldrich) is reacted methylmagnesium bromide and
9 thereafter with acid to provide 2,2,7,7-tetramethyl-dihydro-*iso*-benzofuran of
10 **Formula 71**. The dihydro-*iso*-benzofuran of **Formula 71** is then reacted with
11 *N*-bromosuccinimide (NBS) in tetrahydrofuran (THF) to give 4-bromo-2,2,7,7-
12 tetramethyl-dihydro-*iso*-benzofuran of **Formula 72**.

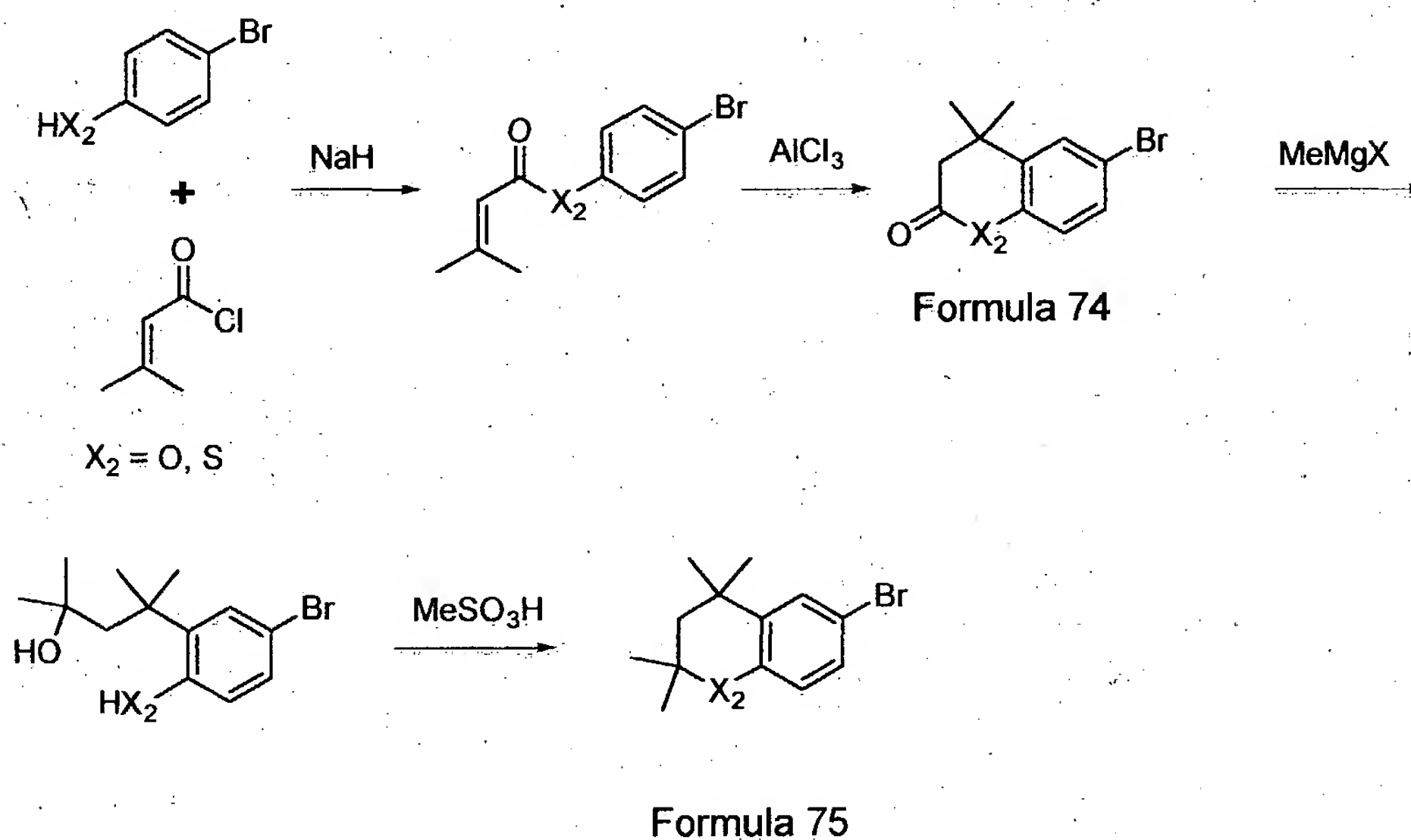
13 In another exemplary sequence of reactions, 4-bromophenol is reacted with
14 3-chloro-2-methyl-prop-1-ene in the presence of strong acid (H₂SO₄), and
15 thereafter with strong base (NaH) to provide 3,3-dimethyl-5-bromo-
16 dihydrobenzofuran of **Formula 73**. The bromo compounds of **Formulas 72** and
17 **73** are subjected to the same sequence of reactions (not shown in **Scheme 7**) as the
18 bromo compounds of **Formulas 4** and **32** of **Reaction Schemes 1** and **2**,
19 respectively, to provide compounds of the invention in accordance with **Formula 1**
20 where the variable **R** is dihydro-*iso*-benzofuran or dihydrobenzofuran radical.



Reaction Scheme 7

Reaction Scheme 8 serves as an example for preparing compounds of the invention which are chroman or thiochroman derivatives, that is where the variable **R** of **Formula 1** is represented by **Formula (f)** and where the dashed line in the formula represents absence of a bond. For the sake of simplicity of illustration the scheme illustrates the synthesis of the compounds of the invention where the variable (**R**₇)_m represents geminal dimethyl groups substituting carbons 2 and 4 of the non-aromatic portion of the chroman or thiochroman nucleus. A detailed description of preparing the 6-bromo thiochroman derivatives shown in **Formulas 74** and **75** when **X**₂ is sulfur (S), through the reactions that are shown in **Reaction Scheme 8** can be found in United States Patent No. 4,980,369. United States Patent No. 4,980,369 is expressly incorporated herein by reference. Analogous

1 6-bromo-4,4-dimethylthiochromans can be made in accordance with the teachings
 2 of United States Patent Nos. 5,015,658 and 5,023,341, both of which are also
 3 incorporated herein by reference. The corresponding 6-bromo chroman derivatives
 4 shown in **Formulas 74** and **75** when X_2 is oxygen (O) can be made by the
 5 reactions shown in the scheme. The bromo compounds of **Formulas 74** and **75** are
 6 subjected to the same sequence of reactions (not shown in **Scheme 7**) as the bromo
 7 compounds of **Formulas 4** and **32** of **Reaction Schemes 1** and **2**, respectively, to
 8 provide compounds of the invention in accordance with **Formula 1** where the
 9 variable **R** is a chroman-2-one, thiochroman-2-one, chroman or thiochroman
 10 radical.



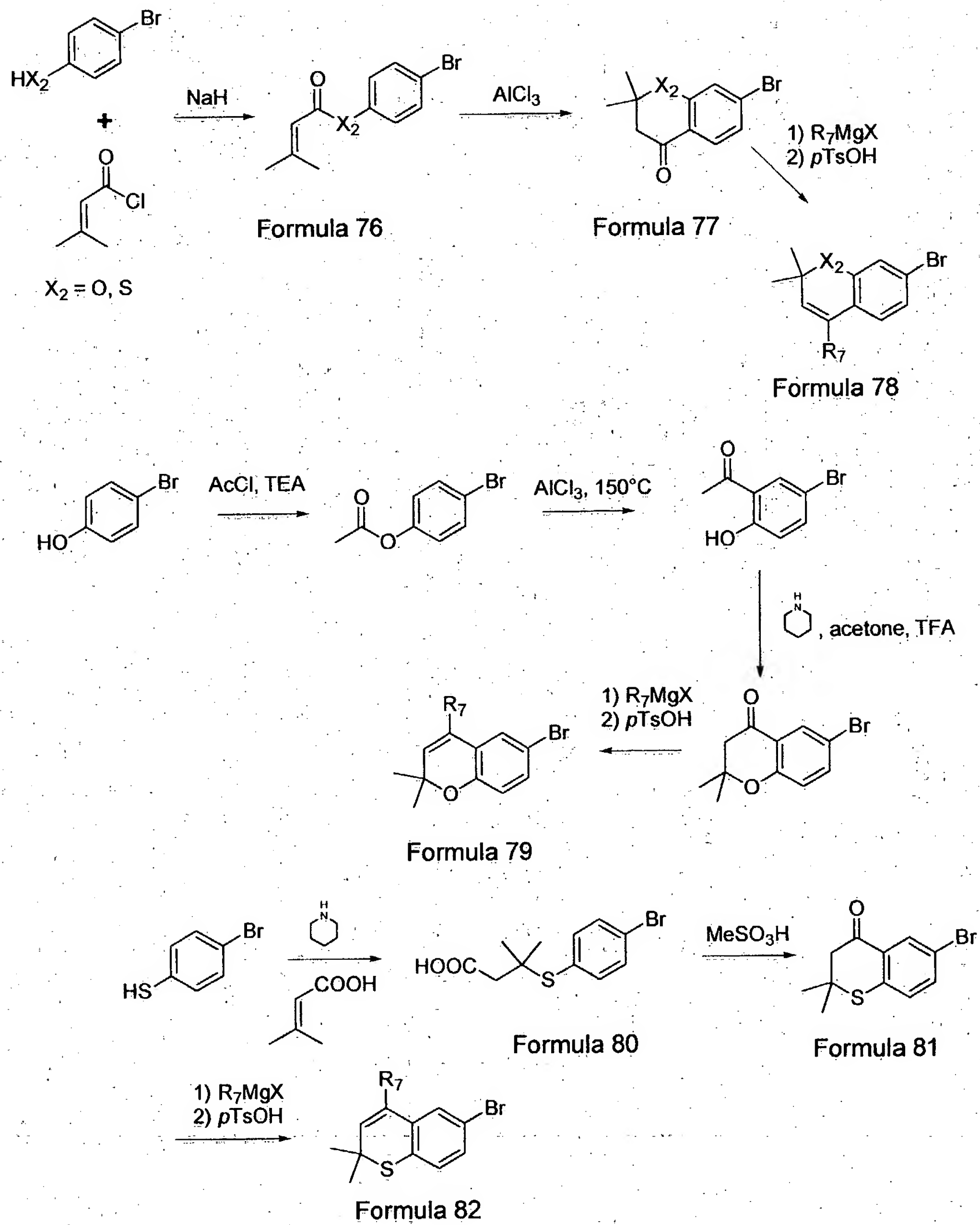
Reaction Scheme 8

1 **Reaction Scheme 9** provides examples for preparing compounds of the
 2 invention which are chromene or thiochromene derivatives, that is where the
 3 variable **R** of **Formula 1** is represented by **Formula (f)** and where the dashed line
 4 represents presence of a bond. For the sake of simplicity of illustration the scheme
 5 illustrates the synthesis of the compounds of the invention where the variable $(R_7)_m$
 6 represents geminal dimethyl groups substituting carbon 2 of the non-aromatic
 7 portion of the chromene or thiochromene nucleus. Thus, in accordance with this
 8 scheme, 4-bromophenol or 4-bromothiophenol is reacted with dimethylacryloyl
 9 chloride to provide the corresponding ester or thioester of **Formula 76**. The ester
 10 or thioester of **Formula 76** is then cyclized under *Friedel Crafts* conditions to
 11 provide the 7-bromo-thiochroman-4-one or the 7-bromo-chroman-4-one of
 12 **Formula 77**. The compound of **Formula 77** is reacted with a Grignard reagent of
 13 the formula R_7MgX (where X is halogen and R_7 is defined as in connection with
 14 **Formula 1**) and then with acid to provide the 7-bromo-2,2-dimethyl-thio-
 15 chromene or corresponding chromene derivative of **Formula 78**.

16 In another exemplary reaction sequence shown in **Reaction Scheme 9**, 4-
 17 bromophenol is reacted with acetyl chloride (AcCl) to provide the corresponding
 18 ester, and the ester made to undergo a *Fries* rearrangement under *Friedel Crafts*
 19 conditions to provide 2-acetyl-4-bromophenol. 2-Acetyl-4-bromophenol is reacted
 20 with acetone in the presence of piperidine and trifluoroacetic acid (TFA) to give 6-
 21 bromo-2,2-dimethyl-chroman-4-one. The latter compound is reacted with the
 22 Grignard reagent of the formula R_7MgX and then with acid to provide the 6-
 23 bromo-2,2-dimethyl-chromene derivative of **Formula 79**.

1 In still another exemplary reaction sequence shown in **Reaction Scheme 9**
2 4-bromo-thiophenol is reacted with 2,2-dimethylacrylic acid in the presence of
3 piperidine to provide an adduct of **Formula 80** that is cyclized by treatment with
4 methylsulfonic acid to give 6-bromo-2,2-dimethyl-thiochroman-4-one of **Formula**
5 **81**. The compound of **Formula 81** is reacted with the Grignard reagent of the
6 formula R_7MgX and then with acid to provide the 6-bromo-2,2-dimethyl-
7 thiochromene derivative of **Formula 82**.

8 The bromo compounds of **Formulas 78, 79 and 82** are subjected to the same
9 sequence of reactions (not shown in **Scheme 9**) as the bromo compounds of
10 **Formulas 4 and 32** of **Reaction Schemes 1 and 2**, respectively, to provide
11 compounds of the invention in accordance with **Formula 1** where the variable **R** is
12 a chromene or a thiochromene radical.



Reaction Scheme 9

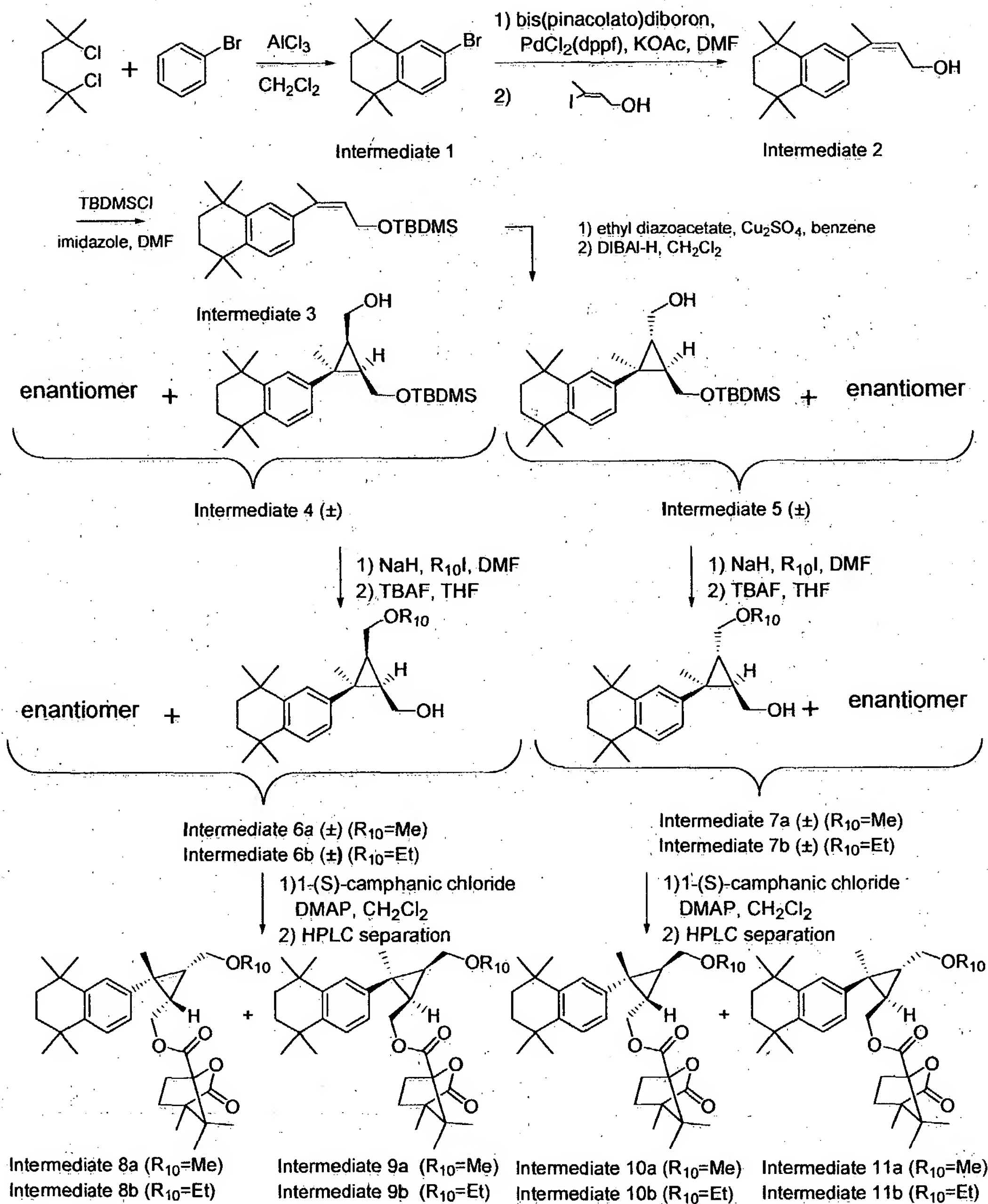
1
2 SPECIFIC EMBODIMENTS OF THE COMPOUNDS OF THE
3 INVENTION

4 Referring now to **Formula 1**, in the preferred compounds of the invention
5 the variable **R** represents a substituted tetrahydronaphthalen-2-yl radical, or a
6 substituted phenyl radical. When **R** is the above-mentioned tetrahydronaphthalen-2-
7 yl radical then **R₇** groups are preferably alkyl of 1 – 6 carbons, more preferably
8 alkyl of 1 to 3 carbons, and even more preferably methyl. Most preferably the
9 variables (**R₇**)_m represents geminal dimethyl groups in the 5 and 8 positions of the
10 tetrahydronaphthalene ring. The variable **R₈** is preferably H or alkyl of 1 to 6
11 carbons, more preferably H or alkyl of 1 to 3 carbons. In the presently most
12 preferred compounds of the invention the aromatic portion of the
13 tetrahydronaphthalene ring is not substituted; in other words **R₈** is H. When **R** is
14 the above-mentioned phenyl group then **R₇** and **R₈** preferably represent alkyl
15 groups of 1 to 6 carbons, even more preferably branch-chained alkyl groups, such
16 as *iso*-propyl.

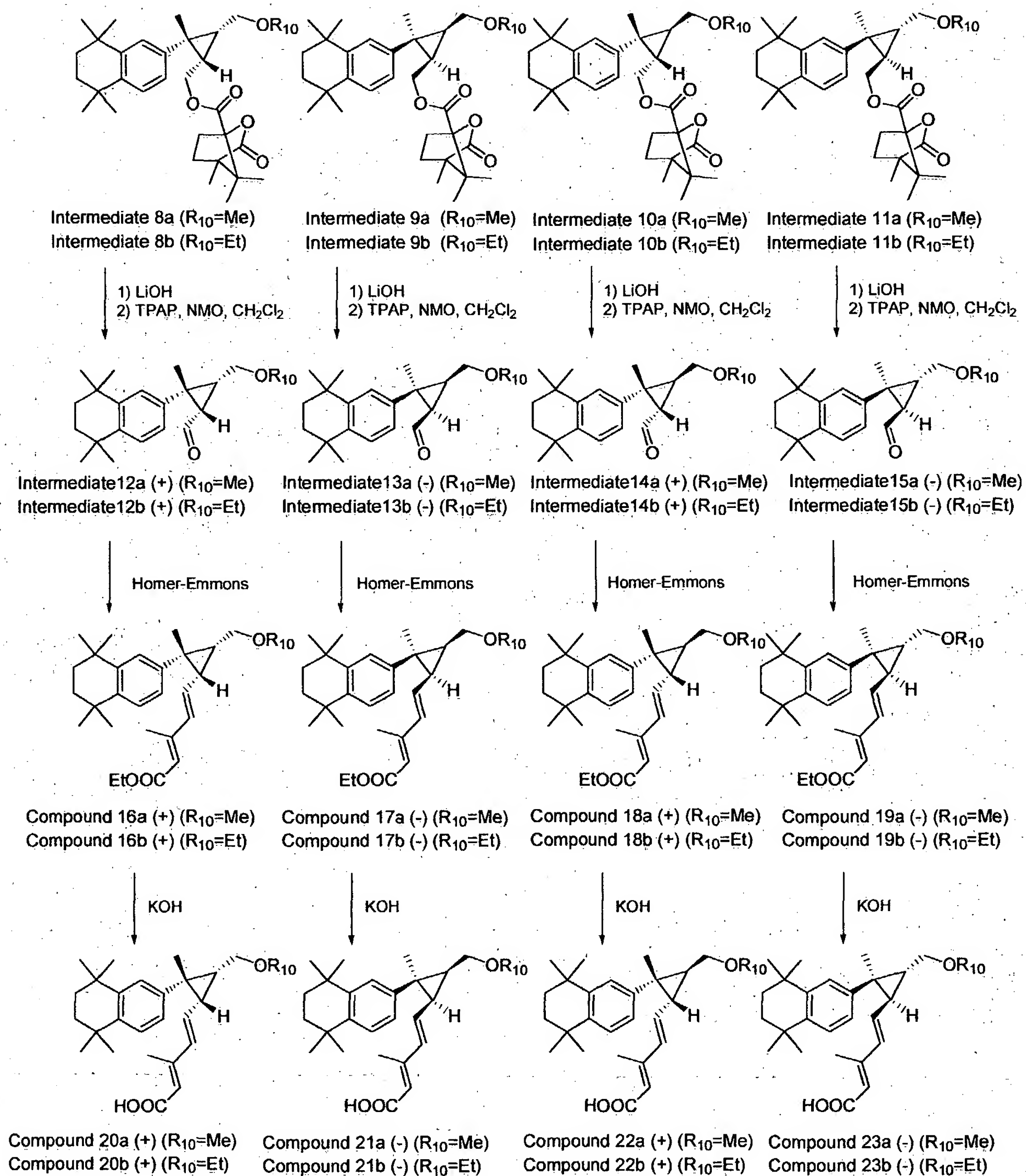
17 Referring still to **Formula 1** the **R₁** group is preferably methyl or ethyl, even
18 more preferably methyl. The **R₂** group preferably is CH₂OCH₃ or CH₂OCH₂CH₃.
19 **R₃** is preferably H, **R₄** is preferably methyl, and **R₅** is preferably, alkyl of 1 to 3
20 carbons, or H, or a pharmaceutically acceptable salt of said compound.

21 The synthesis of the presently most preferred compounds of the invention is
22 shown in **Reaction Schemes 10 and 11** and a detailed description of the

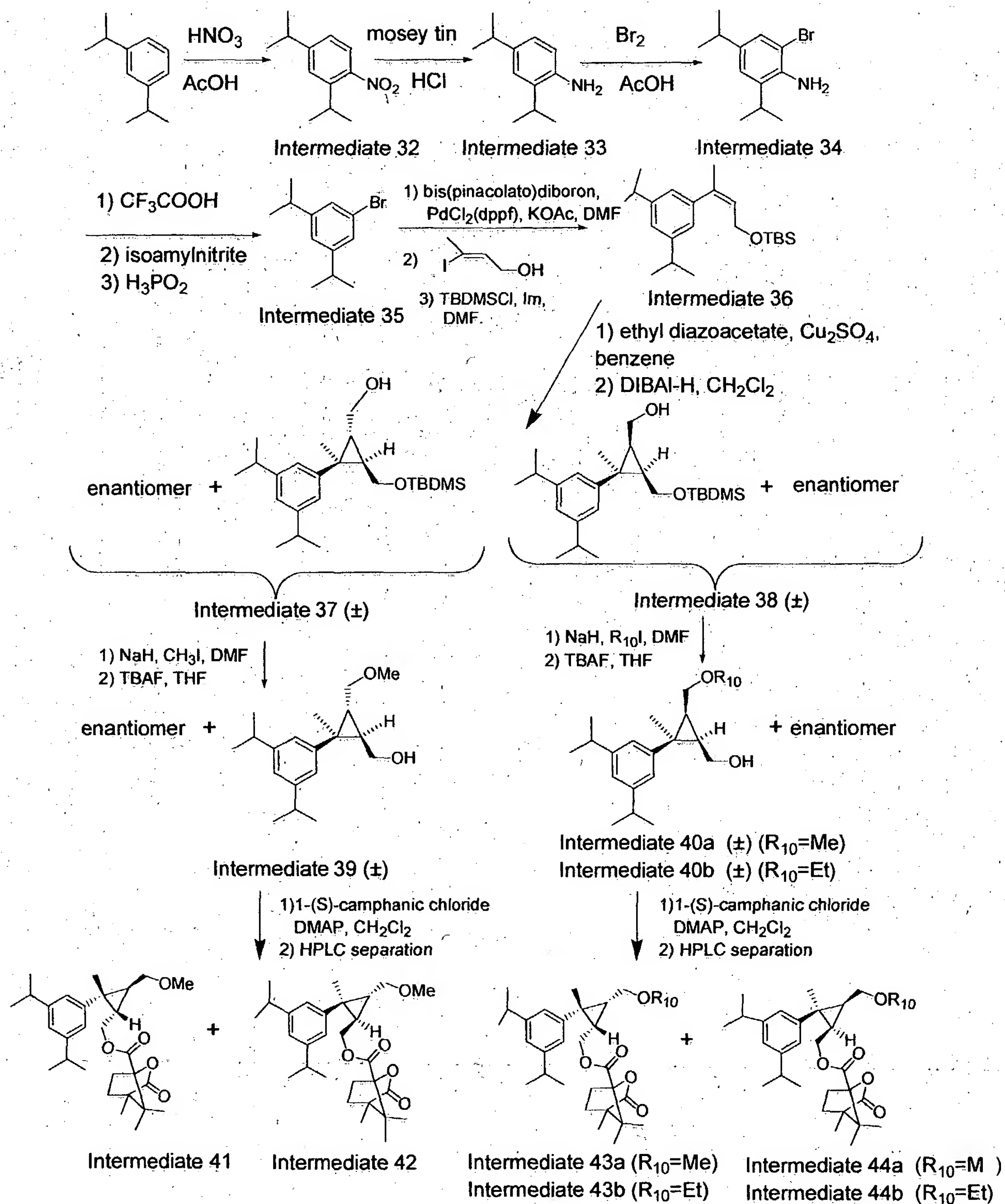
- 1 experimental procedures for synthesizing these most preferred exemplary
- 2 compounds is also provided below.



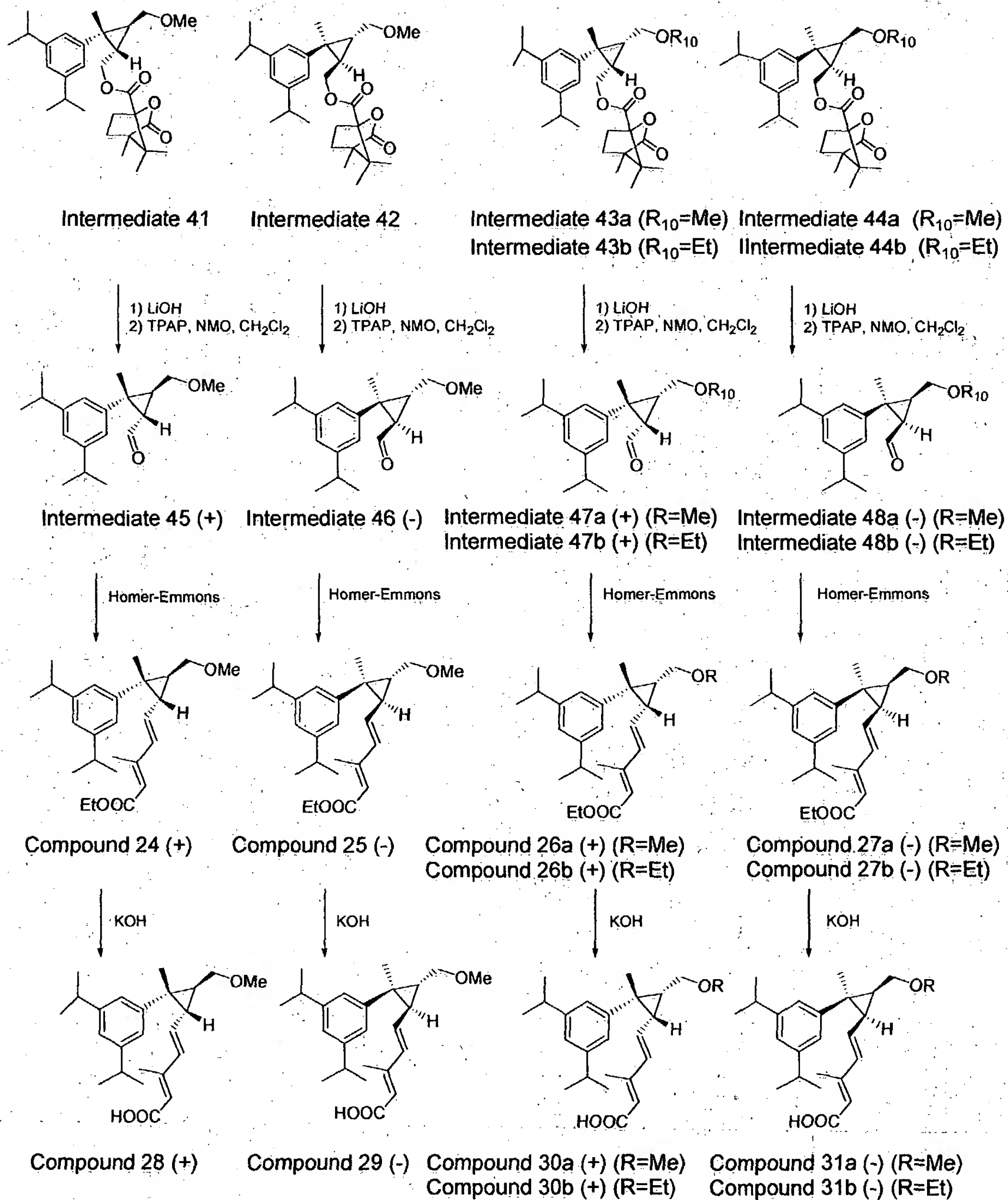
Reaction Scheme 10



Reaction Scheme 10 continued



Reaction Scheme 11



Reaction Scheme 11 continued

Experimental Procedures For Synthesizing the Exemplary Compounds of the
Invention

6-Bromo-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene (Intermediate 1)

Aluminum chloride (700 mg, 5.25 mmol) was added slowly to a solution of 2,5-dichloro-2,5-dimethylhexane (11 g, 60 mmol) in bromobenzene (90 mL) at 0° C. After stirred for 20 min, the mixture was diluted with 100 mL of ether:hexane (1:1), washed with ice-water (1 x 10 mL), 10% HCl (1 x 10 mL) and brine (1 x 10 mL), dried (MgSO₄) and concentrated to afford a brown oil. The crude was then distilled using Coughler distillation to yield the title compound (13.2 g, 83% yield) as a white solid:

¹HNMR (CDCl₃, 300MHz) δ 7.39 (d, *J* = 2.0 Hz, 1H), 7.22 (dd, *J* = 2.0 Hz, 8.1 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 1H), 1.66 (s, 4H), 1.25 (s, 6H).

3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-but-2Z-en-1-ol (Intermediate 2)

Bis(pinacolato)diboron (5.8 g, 22.5 mmol), potassium acetate (4.5 g, 45 mmol) and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium (PdCl₂(dppf)₂) (500 mg, 0.6 mmol) were added to a solution of **Intermediate 1** (4 g, 15 mmol) in 50 mL of DMF under argon. The mixture was then stirred at 80° C for 24 h. After cooling to room temperature, 3-iodo-but-2Z-en-1-ol (6 g, 30 mmol), 2M Na₂CO₃ (30 ml), and PdCl₂(dppf)₂ (500 mg, 0.6 mmol) were added to the mixture, which was then stirred at 80° C for another 24 h. The reaction was finally quenched with water (20 mL) and extracted with ether (3 x 10 mL). The organic

layer was washed with brine (2 x 10 mL), dried (MgSO₄) and concentrated to give a crude brown oil. The crude product was purified by flash chromatography using 20% EtOAc in hexane to give the title compound (3 g, 77% yield) as a colorless oil: ¹HNMR (CDCl₃, 300MHz) δ 7.26 (d, *J* = 8.1 Hz, 1H), 7.09 (d, *J* = 1.8 Hz, 1H), 6.96 (dd, *J* = 1.8 Hz, 8.1 Hz, 1H), 5.69 (t, *J* = 6.3 Hz, 1H), 4.14 (d, *J* = 6.3 Hz, 2H), 2.24 (s, 3H), 1.70 (s, 4H), 1.31 (s, 6H), 1.28 (s, 6H).

tert-Butyldimethyl-[3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-but-2Z-enyloxy]silane (Intermediate 3)

tert-Butyldimethylsilyl chloride (2.7 g, 17.5 mmol) was added to the solution of **Intermediate 2** (3 g, 11.6 mmol) and imidazole (1.6 g, 23.2 mmol) in 10 mL of DMF. The mixture was then stirred for 16 h at room temperature. After quenching with water, the mixture was extracted with ether (3 x 10 mL), washed with brine (1 x 10 mL), dried (MgSO₄) and concentrated to give a crude brown oil. The crude product was purified by flash chromatography using 10% EtOAc in hexane to give the title compound (3 g, 70% yield) as a colorless oil:

¹HNMR (CDCl₃, 300MHz) δ 7.23 (d, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 1.8 Hz, 1H), 6.96 (dd, *J* = 1.8 Hz, 8.1 Hz, 1H), 5.63 (t, *J* = 6.3 Hz, 1H), 4.16 (d, *J* = 6.3 Hz, 2H), 2.21 (s, 3H), 1.70 (s, 4H), 1.29 (s, 6H), 1.28 (s, 6H), 0.86 (s, 9H), 0.00 (s, 6H).

(±)-[(S)-3-(*tert*-Butyldimethylsilanyloxymethyl)-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-methanol (Intermediate 4) and (±)-[(R)-3-(*tert*-butyl-dimethylsilanyloxymethyl)-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-methanol (Intermediate 5)

1 Ethyl diazoacetate (4.5 mL, 42 mmol) in 10 mL of benzene was added
2 slowly with a syringe pump (2ml/h) to a solution of **Intermediate 3** (0.7 g, 1.9
3 mmol) and anhydrous copper (II) sulfate (60 mg, 376 μ mol) in 30 mL of benzene
4 (30 mL) at 80° C. After the addition of ethyl diazoacetate has been completed, the
5 mixture was allowed to stir for 16 h at room temperature in order to decompose the
6 excess of ethyl diazoacetate. The solvent was then evaporated under reduced
7 pressure and the residue was purified by flash chromatography using 2% EtOAc in
8 hexane to yield 1.6 g of a mixture of crude cyclopropyl esters, which were then
9 dissolved in 15 mL of anhydrous THF and cooled to -78° C with a dry ice/acetone
10 bath. To this solution was added DIBAL-H in hexane (1M, 11 mL, 11 mmol) After
11 stirring at -78° C for 2 h, the reaction was quenched with saturated NH₄Cl (4 mL).
12 Celite (4 g) and ether (50 mL) were then added to the mixture and stirring was
13 continued at 0° C until all aluminum salt precipitated out. Inorganic material was
14 removed by filtration, and the solvents were removed under reduced pressure to
15 give a brown oil, which was purified by flash chromatography using 20% EtOAc
16 in hexane to give the title compounds, **Intermediate 4** (232 mg, 29% yield) and
17 **Intermediate 5** (155 mg, 20% yield) as colorless oils :
18 ¹HNMR for **Intermediate 4**: (CDCl₃, 300MHz) δ 7.11 (d, J = 4.8 Hz, 1H), 6.84 (d,
19 J = 0.9 Hz, 1H) 6.70 (dd, J = 3.3 Hz, 6.9 Hz, 1H), 4.08 (dd, J = 3.3 Hz, 6.9 Hz,
20 1H), 3.87-3.92 (m, 1H), 3.10-3.19 (m, 2H), 1.6 (s, 4H), 1.40-1.45 (m, 1H), 1.19-
21 1.28 (m, 16H), 0.82 (s, 9H), 0.00 (d, J = 15.6 Hz, 6H);
22 ¹HNMR for **Intermediate 5**: (CDCl₃, 500MHz) δ 7.26 (d, J = 8.5 Hz, 1H), 7.24
23 (d, J = 2.0 Hz, 1H), 7.12 (dd, J = 2.0 Hz, 8.5 Hz, 1H), 3.87-3.89 (m, 2H), 3.48 (dd,

$J = 7.0$ Hz, 11.0 Hz, 1H), 3.17 (dd, $J = 7.0$ Hz, 11.0 Hz, 1H), 1.73 (s, 3H), 1.46-1.47 (m, 5H), 1.33-1.34 (m, 12H), 1.29 (q, $J = 7.5$ Hz, 1H), 0.91 (s, 9H), 0.19 (d, $J = 9.5$ Hz, 6H).

(±)-[(S)-3-Methoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-cyclopropyl]-methanol (Intermediate 6a)

Sodium hydride (67 mg, 1.68 mmol) was added slowly to a solution of **Intermediate 4** (232 mg, 0.56 mmol) in 5 mL of DMF at 0 °C. After stirring for 10 min, methyl iodide (0.103 mL, 1.68 mmol) was added to the mixture, which was then stirred at room temperature for 16 h. The reaction was quenched with saturated NH_4Cl , extracted with ether (3 x 10 mL), washed with brine (1 x 10 mL), dried (Na_2SO_4) and concentrated to give a crude brown oil. Purification by flash chromatography using 5% EtOAc in hexane afforded the methoxy intermediate still protected with a *tert*-butyldimethylsilyl group (194 mg, 78% yield) as a colorless oil. This colorless oil was then dissolved in 5 mL of anhydrous THF and cooled to 0° C with an ice bath. To this solution was added TBAF in THF (1M, 0.7 mL, 0.7 mmol) and the reaction mixture was allowed to stir at room temperature for 2 h. The reaction was finally quenched with water, extracted with ether (3 x 10 mL), washed with brine (1 x 10 mL), dried (Na_2SO_4) and concentrated to give a crude colorless oil. Purification by flash chromatography using 20% EtOAc in hexane gave the title compound (100 mg, 54% yield) as a colorless oil:

^1H NMR (CDCl_3 , 500MHz) δ 7.17 (d, $J = 8.5$ Hz, 1H), 6.93 (d, $J = 2.0$ Hz, 1H), 6.77 (dd, $J = 2.0$ Hz, 8.5 Hz, 1H), 3.94 (dd, $J = 5.5$ Hz, 10.5 Hz, 1H), 3.79 (dd, $J =$

1 5.5 Hz, 10.5 Hz, 1H), 3.31 (s, 3H), 3.10 (dd, $J = 10.0$ Hz, 11.0 Hz, 1H), 3.00 (dd, J
 2 = 10.0 Hz, 11.0 Hz, 1H), 1.65 (s, 4H), 1.39-1.50 (m, 2H), 1.30 (s, 3H), 1.25 (s,
 3 6H), 1.24 (s, 6H).

4 (±)-[(S)-3-Ethoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-
 5 naphthalen-2-yl)-cyclopropyl]-methanol (Intermediate 6b)

6 Following a procedure similar to that for the preparation of **Intermediate 6a**
 7 using **Intermediate 4** as the starting material and ethyl iodide as alkylating reagent
 8 yielded the title compound as a colorless oil (69 mg, 78% yield):

9 ^1H NMR (CDCl_3 , 300MHz) δ 7.07 (d, $J = 8.4$ Hz, 1H), 6.84 (d, $J = 2.1$ Hz, 1H),
 10 6.67 (dd, $J = 2.1$ Hz, 8.4 Hz, 1H), 3.74-3.89 (m, 2H), 3.25-3.41 (m, 1H), 2.89-3.05
 11 (m, 2H), 1.56 (s, 4H), 1.28-1.43 (m, 2H), 1.21 (s, 3H), 1.55 (s, 12H), 1.1 (t, $J = 6.9$
 12 Hz, 3H).

13 (±)-[(R)-3-Methoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-
 14 naphthalen-2-yl)-cyclopropyl]-methanol (Intermediate 7a)

15 Following a procedure similar to that for the preparation of **Intermediate 6a**
 16 using **Intermediate 5** as the starting material and methyl iodide as the alkylating
 17 reagent provided the title compound as a colorless oil (67 mg, 40% yield) :

18 ^1H NMR (CDCl_3 , 500MHz) δ 7.18-7.20 (m, 2H), 7.03 (dd, $J = 1.5$ Hz, 7.5 Hz, 1H),
 19 3.55-3.61 (m, 2H), 3.41 (s, 3H), 3.22-3.21 (m, 2H), 1.65 (s, 3H), 1.34-1.42 (m,
 20 5H), 1.24 (s, 12H), 1.09-1.13 (m, 1H).

21 (±)-[(R)-3-Ethoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-
 22 naphthalen-2-yl)-cyclopropyl]-methanol (Intermediate 7b)

Following a procedure similar to that for the preparation of **Intermediate 6a** using **Intermediate 5** as the starting material and ethyl iodide as the alkylating reagent provided the title compound (65 mg, 81% yield) as a colorless oil:

¹HNMR (CDCl₃, 300MHz) δ 7.12-7.14 (m, 2H), 6.99 (dd, *J* = 1.8 Hz, 8 Hz, 1H), 3.46-3.56 (m, 4H), 3.20 (d, *J* = 7.2 Hz, 2H), 1.59 (s, 4H), 1.34-1.37 (m, 4H), 1.03-1.19 (m, 15H), 1.02-1.15 (m, 1H).

(1S, 2R, 3R)-3-Methoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropylmethyl 4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylate (**Intermediate 8a**) and (1R, 2S, 3S)-3-Methoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropylmethyl 4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylate (**Intermediate 9a**)

1-(S)-(-)-Camphanic chloride (113 mg, 0.75 mmol) and *N,N*-dimethylaminopyridine (113 mg, 0.93 mmol) were added to a solution of **Intermediate 6a** (100 mg, 0.46 mmol) in 5 mL of dichloromethane. After stirring at room temperature for 16 h, the mixture was extracted with dichloromethane (2 x 10 mL), washed with water (1 x 10 mL), dried (Na₂SO₄) and concentrated to give a crude colorless oil. Purification by column chromatography using 10% EtOAc in hexane afforded a mixture of **Intermediates 8a** and **9a** in 1:1 ratio (162 mg, 89% yield). Separation of this mixture with normal phase HPLC (Whatman, Partisil-10-PAC HPLC column) using 8% EtOAc in hexane as eluent yielded **Intermediate 8a** (83 mg, 45% yield) and **Intermediate 9a** (79 mg, 44% yield) as colorless oils:

¹HNMR for **Intermediate 8a**: (CDCl₃, 500MHz) δ 7.23 (d, *J* = 2.0 Hz, 1H), 7.20

1 (d, $J = 8.5$ Hz, 1H), 6.97 (dd, $J = 2.0$ Hz, 8.5 Hz, 1H), 4.25-4.29 (m, 1H), 3.97-4.00
 2 (m, 1H), 3.32-3.24 (m, 5H), 2.41-2.46 (m, 1H), 1.94-2.06 (m, 1H), 1.90-1.95 (m,
 3 1H), 1.66-1.72 (m, 4H), 1.56 (s, 4H), 1.37-1.45 (m, 2H), 1.34 (s, 3H), 1.26 (s, 6H),
 4 1.25 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 0.99 (s, 3H);

5 ¹HNMR for **Intermediate 9a**: (CDCl₃, 500MHz) δ 7.22 (d, $J = 2.0$ Hz, 1H), 7.18
 6 (d, $J = 8.5$ Hz, 1H), 6.99 (dd, $J = 2.0$ Hz, 8.5 Hz, 1H), 4.26-4.30 (m, 1H), 3.97-3.99
 7 (m, 1H), 3.31-3.28 (m, 5H), 2.42-2.46 (m, 1H), 1.94-2.06 (m, 1H), 1.90-1.95 (m,
 8 1H), 1.66-1.72 (m, 4H), 1.56 (s, 4H), 1.37-1.45 (m, 2H), 1.34 (s, 3H), 1.26 (s, 6H),
 9 1.25 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 0.99 (s, 3H).

10 (1S, 2R, 3R)-3-Ethoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-
 11 naphthalen-2-yl)-cyclopropylmethyl 4,7,7-trimethyl-3-oxo-2-oxa-
 12 bicyclo[2.2.1]heptane-1-carboxylate (**Intermediate 8b**) and (1R, 2S, 3S)-3-
 13 Ethoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-
 14 yl)-cyclopropylmethyl 4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-
 15 carboxylate (**Intermediate 9b**)

16 Following a procedure similar to that for the preparations of **Intermediates**
 17 **8a** and **9a** but using **Intermediate 6b** as the starting material afforded
 18 **Intermediate 8b** (62 mg, 50% yield) and **Intermediate 9b** (60 mg, 49% yield) as
 19 colorless oils:

20 ¹HNMR for **Intermediate 8b**: (CDCl₃, 500MHz) δ 7.23 (d, $J = 2.0$ Hz, 1H), 7.20
 21 (d, $J = 8.5$ Hz, 1H), 6.97 (dd, $J = 2.0$ Hz, 8.5 Hz, 1H), 4.25-4.29 (m, 1H), 3.97-4.00
 22 (m, 1H), 3.40 (q, $J = 6.9$ Hz, 2H), 3.32-3.24 (m, 2H), 2.41-2.46 (m, 1H), 1.94-2.06
 23 (m, 1H), 1.90-1.95 (m, 1H), 1.66-1.72 (m, 4H), 1.56 (s, 4H), 1.37-1.45 (m, 2H),

1 1.34 (s, 3H), 1.19-1.26 (m, 9H), 1.18 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 0.99 (s,
2 3H);

3 ¹HNMR for **Intermediate 9b**: (CDCl₃, 500MHz) δ 7.22 (d, *J* = 2.0 Hz, 1H), 7.18
4 (d, *J* = 8.5 Hz, 1H), 6.99 (dd, *J* = 2.0 Hz, 8.5 Hz, 1H), 4.26-4.30 (m, 1H), 3.97-3.99
5 (m, 1H), 3.40 (q, *J* = 6.9 Hz, 2H), 3.31-3.28 (m, 2H), 2.42-2.46 (m, 1H), 1.94-2.06
6 (m, 1H), 1.90-1.95 (m, 1H), 1.66-1.72 (m, 4H), 1.56 (s, 4H), 1.37-1.45 (m, 2H),
7 1.34 (s, 3H), 1.19-1.26 (m, 9H), 1.18 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 0.99 (s,
8 3H).

9 (1S, 2R, 3S)-3-Methoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-
10 tetrahydro-naphthalen-2-yl)-cyclopropylmethyl 4,7,7-trimethyl-3-oxo-2-oxa-
11 bicyclo[2.2.1]heptane-1-carboxylate (**Intermediate 10a**) and (1R, 2S, 3R)-3-
12 Methoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-
13 yl)-cyclopropylmethyl 4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-
14 carboxylate (**Intermediate 11a**)

15 Following a procedure similar to that for the preparation of **Intermediates**
16 **8a** and **9a** while using **Intermediate 7a** as the starting material and 10% EtOAc in
17 hexane as normal phase HPLC eluent afforded **Intermediate 10a** (46 mg, 36%
18 yield) and **Intermediate 11a** (45 mg, 36% yield) from **7a** as colorless oils :

19 ¹HNMR for **Intermediate 10a**: (CDCl₃, 500MHz) δ 7.18 (d, *J* = 8.5 Hz, 1H), 7.10
20 (d, *J* = 2.0 Hz, 1H), 6.95 (dd, *J* = 2.0 Hz, 8.5 Hz, 1H), 3.95-3.99 (m, 1H), 3.80-3.84
21 (m, 1H), 3.59-3.62 (m, 1H), 3.51-3.55 (m, 1H), 3.40 (s, 3H), 2.41-2.46 (m, 1H),
22 1.94-2.06 (m, 1H), 1.90-1.95 (m, 1H), 1.66-1.72 (m, 4H), 1.56 (s, 4H), 1.37-1.45

1 (m, 2H), 1.34 (s, 3H), 1.26 (s, 6H), 1.25 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 0.99 (s,
2 3H);

3 ¹HNMR for **Intermediate 11a**: (CDCl₃, 500MHz) δ 7.16 (d, *J* = 8.5 Hz, 1H), 7.15
4 (d, *J* = 2.0 Hz, 1H), 7.02 (dd, *J* = 2.0 Hz, 8.5 Hz, 1H), 3.90-3.94 (m, 1H), 3.72-3.76
5 (m, 1H), 3.51-3.55 (m, 1H), 3.44-3.48 (m, 1H), 2.27-2.33 (m, 1H), 1.94-2.06 (m,
6 1H), 1.90-1.95 (m, 1H), 1.66-1.72 (m, 4H), 1.56 (s, 4H), 1.37-1.45 (m, 2H), 1.34
7 (s, 3H), 1.26 (s, 6H), 1.25 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 0.99 (s, 3H).

8 (1S, 2R, 3S)-3-Ethoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-
9 naphthalen-2-yl)-cyclopropylmethyl 4,7,7-trimethyl-3-oxo-2-oxa-
10 bicyclo[2.2.1]heptane-1-carboxylate (**Intermediate 10b**) and (1R, 2S, 3R)-3-
11 Ethoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-
12 yl)-cyclopropylmethyl 4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-
13 carboxylate (**Intermediate 11b**)

14 Following a procedure similar to that for the preparation of **Intermediates**
15 **8a** and **9a** but using **intermediate 7b** as the starting material and 10% EtOAc in
16 hexane as normal phase HPLC eluent afforded **Intermediate 10b** (49 mg, 42%
17 yield) and **Intermediate 11b** (48 mg, 42% yield) from **7b** as colorless oils:

18 ¹HNMR for **Intermediate 10b**: (CDCl₃, 300MHz) δ 7.25 (d, *J* = 8.5 Hz, 1H), 7.18
19 (d, *J* = 2.0 Hz, 1H), 7.02 (dd, *J* = 2.0 Hz, 8.5 Hz, 1H), 3.95-3.99 (m, 1H), 3.78-3.85
20 (m, 1H), 3.51-3.67 (m, 4H), 2.41-2.46 (m, 1H), 1.94-2.06 (m, 1H), 1.90-1.95 (m,
21 1H), 1.66-1.72 (m, 4H), 1.56 (s, 4H), 1.37-1.45 (m, 2H), 1.34 (s, 3H), 1.15-1.26 (s,
22 12H), 1.1 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H);

23 ¹HNMR for **Intermediate 11b**: (CDCl₃, 300MHz) δ 7.25 (d, *J* = 8.5 Hz, 1H), 7.18

1 (d, $J = 2.0$ Hz, 1H), 7.02 (dd, $J = 2.0$ Hz, 8.5 Hz, 1H), 3.95-4.01 (m, 1H), 3.78-3.84
 2 (m, 1H), 3.51-3.67 (m, 4H), 2.33-2.42 (m, 1H), 1.94-2.02 (m, 1H), 1.89-1.94 (m,
 3 1H), 1.66-1.72 (m, 4H), 1.56 (s, 4H), 1.37-1.45 (m, 2H), 1.34 (s, 3H), 1.15-1.26 (s,
 4 12H), 1.1 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H).

5 (+)-(1S, 2R, 3R)-3-Methoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-
 6 tetrahydro-naphthalen-2-yl)-cyclopropanecarbaldehyde (Intermediate 12a)

7 Potassium hydroxide solution (1N, 1 mL) was added to a solution of
 8 **Intermediate 8a** (83 mg, 0.21 mmol) in 4 mL of THF/MeOH (1 :1) at room
 9 temperature. After stirring for an hour, the mixture was diluted with ethyl acetate
 10 (10 mL) and acidified with 1 mL of 1 N HCl at 0° C. The organic layer was then
 11 washed with brine (1 x 5 mL), dried (Na₂SO₄) and concentrated. The residue was
 12 purified by flash chromatography using 20% EtOAc in hexane to give the
 13 corresponding alcohol (45 mg, 100% yield). This alcohol was subsequently
 14 dissolved in dichloromethane (5 mL) and acetonitrile (0.5 mL). To this solution
 15 was added molecular sieve (45 mg), 4-methylmorpholine *N*-oxide (23 mg, 0.40
 16 mmol) and tetrapropylammonium perruthenate (5 mg, 0.01 mmol). After stirring at
 17 room temperature for 45 min, the solvent was then removed under reduced
 18 pressure and the residue was purified by flash chromatography using 10% EtOAc
 19 in hexane to obtain the title compound in optically pure form (44 mg, 99% yield)
 20 as a colorless oil:

21 ¹H NMR (CDCl₃, 300 MHz) δ 8.8 (d, $J = 7.5$ Hz, 1H), 7.15-7.18 (m, 2H), 6.90 (dd,
 22 $J = 4$ Hz, 14 Hz, 1H), 3.62-3.68 (m, 1H), 3.26-3.41 (m, 1H), 3.26 (s, 3H), 1.88-
 23 1.97 (m, 2H), 1.60 (s, 4H), 1.35 (s, 3H), 1.19 (s, 12H).

1 (+)-(1S, 2R, 3R)-3-Ethoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-
2 tetrahydro-naphthalen-2-yl)-cyclopropanecarbaldehyde (Intermediate 12b)

3 Following a procedure similar to that for the preparation of **Intermediate**
4 **12a** but using **Intermediate 8b** as the starting material afforded the title compound
5 (36 mg, 97% yield) as a colorless oil:

6 ¹HNMR (CDCl₃, 300MHz) δ 8.8 (d, *J* = 7.5 Hz, 1H), 7.15-7.18 (m, 2H), 6.90 (dd,
7 *J* = 4 Hz, 14 Hz, 1H), 3.67-3.73 (m, 1H), 3.31-3.45 (m, 3H), 1.88-1.97 (m, 2H),
8 1.60 (s, 4H), 1.35 (s, 3H), 1.19 (s, 12H), 1.11 (t, *J* = 7 Hz, 3H).

9 (-)-(1R, 2S, 3S)-3-Methoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-
10 tetrahydro-naphthalen-2-yl)-cyclopropanecarbaldehyde (Intermediate 13a)

11 Following a procedure similar to that for the preparation of **Intermediate**
12 **12a** but using **Intermediate 9a** as the starting material afforded the title compound
13 (42 mg, 99% yield) as a colorless oil:

14 ¹HNMR (CDCl₃, 300MHz) δ 8.8 (d, *J* = 7.5 Hz, 1H), 7.15-7.18 (m, 2H), 6.90 (dd,
15 *J* = 4 Hz, 14 Hz, 1H), 3.62-3.68 (m, 1H), 3.26-3.41 (m, 1H), 3.26 (s, 3H), 1.88-
16 1.97 (m, 2H), 1.60 (s, 4H), 1.35 (s, 3H), 1.19 (s, 12H).

17 (-)-(1R, 2S, 3S)-3-Ethoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-
18 tetrahydro-naphthalen-2-yl)-cyclopropanecarbaldehyde (Intermediate 13b)

19 Following a procedure similar to that for the preparation of **Intermediate**
20 **12a** but using **Intermediate 9b** as the starting material afforded the title compound
21 (36 mg, 94% yield) as a colorless oil:

¹HNMR (CDCl₃, 300MHz) δ 8.8 (d, *J* = 7.5 Hz, 1H), 7.15-7.18 (m, 2H), 6.90 (dd, *J* = 4 Hz, 14 Hz, 1H), 3.67-3.73 (m, 1H), 3.31-3.45 (m, 3H), 1.88-1.97 (m, 2H), 1.60 (s, 4H), 1.35 (s, 3H), 1.19 (s, 12H), 1.11 (t, *J* = 7 Hz, 3H).

(+)-(1S, 2R, 3S)-3-Methoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropanecarbaldehyde (Intermediate 14a)

Following a procedure similar to that for the preparation of **Intermediate 12a** but using **Intermediate 10a** as the starting material afforded the title compound (23 mg, 84% yield) as a colorless oil:

¹HNMR (CDCl₃, 300MHz) δ 8.38 (d, *J* = 7.8 Hz, 1H), 7.11-7.19 (m, 2H), 6.90 (dd, *J* = 2.1 Hz, 8.1 Hz, 1H), 3.47-3.65 (m, 2H), 3.36 (s, 3H), 2.30-2.37 (m, 1H), 1.67-1.71 (m, 1H), 1.58 (s, 4H), 1.38 (s, 3H), 1.16-1.19 (m, 12H).

(+)-(1S, 2R, 3S)-3-Ethoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropanecarbaldehyde (Intermediate 14b)

Following a procedure similar to that for the preparation of **Intermediate 12a** but using **Intermediate 10b** as the starting material afforded the title compound (27 mg, 98% yield) as a colorless oil:

¹HNMR (CDCl₃, 300MHz) δ 8.37 (d, *J* = 7.2 Hz, 1H), 7.11-7.19 (m, 2H), 6.90 (dd, *J* = 2.1 Hz, 8.1 Hz, 1H), 3.46-3.67 (m, 4H), 2.32-2.37 (m, 1H), 1.67-1.71 (m, 1H), 1.59 (s, 4H), 1.38 (s, 3H), 1.19 (s, 6H), 1.18 (s, 6H), 1.16 (t, *J* = 6.5 Hz, 3H).

(-)-(1R, 2S, 3R)-3-Methoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropanecarbaldehyde (Intermediate 15a)

Following a procedure similar to that for the preparation of **Intermediate 12a** but using **Intermediate 11a** as the starting material afforded the title compound (25 mg, 81% yield) as a colorless oil:

¹HNMR (CDCl₃, 300MHz) δ 8.38 (d, *J* = 7.8 Hz, 1H), 7.11-7.19 (m, 2H), 6.90 (dd, *J* = 2.1 Hz, 8.1 Hz, 1H), 3.47-3.65 (m, 2H), 3.36 (s, 3H), 2.30-2.37 (m, 1H), 1.67-1.71 (m, 1H), 1.58 (s, 4H), 1.38 (s, 3H), 1.16-1.19 (m, 12H).

(-)-(1R, 2S, 3R)-3-Ethoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropanecarbaldehyde (**Intermediate 15b**)

Following a procedure similar to that for the preparation of **Intermediate 12a** but using **Intermediate 11b** as the starting material afforded the title compound (25 mg, 97% yield) as a colorless oil:

¹HNMR (CDCl₃, 300MHz) δ 8.37 (d, *J* = 7.2 Hz, 1H), 7.11-7.19 (m, 2H), 6.90 (dd, *J* = 2.1 Hz, 8.1 Hz, 1H), 3.46-3.67 (m, 4H), 2.32-2.37 (m, 1H), 1.67-1.71 (m, 1H), 1.59 (s, 4H), 1.38 (s, 3H), 1.19 (s, 6H), 1.18 (s, 6H), 1.16 (t, *J* = 6.5 Hz, 3H).

Ethyl (+)-(1S, 2R, 3R)-5-[3-methoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoate (**Compound 16a**)

n-Butyl lithium in hexane (1.6 M, 1.25 mL, 2.0 mmol) was added to a solution of triethylphosphono-3-methyl-2*E*-butenoate (available from Aldrich) (528 mg, 2.0 mmol) in 5 mL of THF and 3 mL of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) at -78 °C. After stirring for 5 min, a solution of **Intermediate 12a** (44 mg, 0.20 mmol) in 1 mL of THF was added by cannulation. The resulting solution was stirred at -78 °C for 2 h before it was quenched with

saturated NH_4Cl . The mixture was then extracted with ether (3 x 5 mL), washed with brine (1 x 10 mL), dried (Na_2SO_4) and concentrated to give a crude colorless oil. Purification by column chromatography using 5% EtOAc in hexane afforded the title compound (59 mg, 70% yield) as a white solid:

^1H NMR (CDCl_3 , 300MHz) δ 7.17 (d, $J = 8.4$ Hz, 1H), 7.07 (d, $J = 1.8$ Hz, 1H), 6.88 (dd, $J = 1.8$ Hz, 1.8 Hz, 1H), 6.25 (d, $J = 15.6$ Hz, 1H), 5.61 (s, 1H), 5.44 (dd, $J = 10.8$ Hz, 15.6 Hz, 1H), 4.07 (q, $J = 7.2$ Hz, 2H), 3.29-3.35 (m, 1H), 3.23 (s, 3H), 3.10-3.16 (dd, $J = 7.8$ Hz, 2.4 Hz, 1H), 2.02 (s, 3H), 1.77-1.83 (m, 1H), 1.59 (s, 4H), 1.52-1.57 (m, 1H), 1.30 (s, 3H), 1.18-1.22 (m, 15H).

Ethyl (+)-(1S, 2R, 3R)-5-[3-ethoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-3-methyl-penta-2E,4E-dienoate
(**Compound 16b**)

Following a procedure similar to that for the preparation of **Compound 16a** but using **Intermediate 12b** as the starting material afforded the title compound (42 mg, 88% yield) as a white solid:

^1H NMR (CDCl_3 , 500MHz) δ 7.12 (d, $J = 8.4$ Hz, 1H), 7.07 (d, $J = 1.8$ Hz, 1H), 6.90 (dd, $J = 1.8$ Hz, 1.8 Hz, 1H), 6.23 (d, $J = 15.6$ Hz, 1H), 5.61 (s, 1H), 5.44 (dd, $J = 10.8$ Hz, 15.6 Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.32-3.37 (m, 3H), 3.15-3.19 (m, 1H), 2.02 (s, 3H), 1.77-1.83 (m, 1H), 1.59 (s, 4H), 1.52-1.57 (m, 1H), 1.30 (s, 3H), 1.17-1.30 (m, 18H).

Ethyl (-)-(1R, 2S, 3S)-5-[3-methoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-3-methyl-penta-2E,4E-dienoate
(**Compound 17a**)

Following a procedure similar to that for the preparation of **Compound 16a** but using **Intermediate 13a** as the starting material afforded the title compound (53 mg, 66% yield) as a white solid:

¹HNMR (CDCl₃, 500MHz) δ 7.17 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 1.8 Hz, 1H), 6.88 (dd, *J* = 1.8 Hz, 1.8 Hz, 1H), 6.25 (d, *J* = 15.6 Hz, 1H), 5.61 (s, 1H), 5.44 (dd, *J* = 10.8 Hz, 15.6 Hz, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.29-3.35 (m, 1H), 3.23 (s, 3H), 3.10-3.16 (dd, *J* = 7.8 Hz, 2.4 Hz, 1H), 2.02 (s, 3H), 1.77-1.83 (m, 1H), 1.59 (s, 4H), 1.52-1.57 (m, 1H), 1.30 (s, 3H), 1.18-1.22 (m, 15H).

Ethyl (-)-(1R, 2S, 3S)-5-[3-ethoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoate
(**Compound 17b**)

Following a procedure similar to that for the preparation of **Compound 16a** but using **Intermediate 13b** as the starting material afforded the title compound (44 mg, 92% yield) as a white solid:

¹HNMR (CDCl₃, 500MHz) δ 7.12 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 1.8 Hz, 1H), 6.90 (dd, *J* = 1.8 Hz, 1.8 Hz, 1H), 6.23 (d, *J* = 15.6 Hz, 1H), 5.61 (s, 1H), 5.44 (dd, *J* = 10.8 Hz, 15.6 Hz, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.32-3.37 (m, 3H), 3.15-3.19 (m, 1H), 2.02 (s, 3H), 1.77-1.83 (m, 1H), 1.59 (s, 4H), 1.52-1.57 (m, 1H), 1.30 (s, 3H), 1.17-1.30 (m, 18H).

Ethyl (+)-(1S, 2R, 3S)-5-[3-methoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoate
(**Compound 18a**)

Following a procedure similar to that for the preparation of **Compound 16a** but using **Intermediate 14a** as the starting material afforded the title compound (32 mg, 76 % yield) as a white solid:

¹HNMR (CDCl₃, 300MHz) δ 7.14 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 2.1 Hz, 1H), 6.93 (dd, *J* = 2.1 Hz, 8.4 Hz, 1H), 6.10 (d, *J* = 15.6 Hz, 1H), 5.54 (s, 1H), 5.17 (dd, *J* = 9.6 Hz, 15.3 Hz, 1H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.53-3.58 (m, 2H), 3.35 (s, 3H), 1.91 (s, 3H), 1.47-1.58 (m, 6H), 1.34 (s, 3H), 1.11-1.22 (m, 18H).

Ethyl (+)-(1S, 2R, 3S)-5-[3-ethoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoate

(Compound 18b)

Following a procedure similar to that for the preparation of **Compound 16a** but using **Intermediate 14b** as the starting material afforded the title compound (38 mg, 74% yield) as a white solid:

¹HNMR (CDCl₃, 300MHz) δ 7.14 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 2.1 Hz, 1H), 6.94 (dd, *J* = 2.1 Hz, 8.4 Hz, 1H), 6.10 (d, *J* = 15.6 Hz, 1H), 5.54 (s, 1H), 5.17 (dd, *J* = 9.6 Hz, 15.3 Hz, 1H), 4.05 (q, *J* = 7.0 Hz, 2H), 3.45-3.66 (m, 4H), 1.91 (s, 3H), 1.47-1.58 (m, 6H), 1.34 (s, 3H), 1.11-1.22 (m, 21H).

Ethyl (-)-(1R, 2S, 3R)-5-[3-methoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoate

(Compound 19a)

Following a procedure similar to that for the preparation of **Compound 16a** but using **Intermediate 15a** as the starting material afforded the title compound (34 mg, 75% yield) as a white solid:

¹HNMR (CDCl₃, 300MHz) δ 7.14 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 2.1 Hz, 1H), 6.93 (dd, *J* = 2.1 Hz, 8.4 Hz, 1H), 6.10 (d, *J* = 15.6 Hz, 1H), 5.54 (s, 1H), 5.17 (dd, *J* = 9.6 Hz, 15.3 Hz, 1H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.53-3.58 (m, 2H), 3.35 (s, 3H), 1.91 (s, 3H), 1.47-1.58 (m, 6H), 1.34 (s, 3H), 1.11-1.22 (m, 18H).

Ethyl (-)-(1R, 2S, 3R)-5-[3-ethoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoate
(**Compound 19b**)

Following a procedure similar to that for the preparation of **Compound 16a** but using **Intermediate 15b** as the starting material afforded the title compound (35 mg, 73% yield) as a white solid:

¹HNMR (CDCl₃, 300MHz) δ 7.14 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 2.1 Hz, 1H), 6.94 (dd, *J* = 2.1 Hz, 8.4 Hz, 1H), 6.10 (d, *J* = 15.6 Hz, 1H), 5.54 (s, 1H), 5.17 (dd, *J* = 9.6 Hz, 15.3 Hz, 1H), 4.05 (q, *J* = 7.0 Hz, 2H), 3.45-3.66 (m, 4H), 1.91 (s, 3H), 1.47-1.58 (m, 6H), 1.34 (s, 3H), 1.11-1.22 (m, 21H).

(+)-(1S, 2R, 3R)-5-[3-Methoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoic acid
(**Compound 20a**)

Sodium hydroxide solution (1N, 1mL) was added to a solution of **Compound 16a** (59 mg, 0.13 mmol) in 4 mL of THF/MeOH (1 :1) at 50° C. After stirring at 50° C for 16 h, the mixture was diluted with ethyl acetate (10 mL) and acidified with 1 mL of 1 HCl at 0° C. The organic layer was then washed with brine (1 x 5 mL), dried (Na₂SO₄) and concentrated. The residue was purified by

flash chromatography using 30% EtOAc in hexane to give the title compound (43 mg, 79% yield) as a white solid:

¹HNMR (CDCl₃, 300MHz) δ 7.20 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 1.8 Hz, 1H), 7.04 (dd, *J* = 1.8 Hz, 8.4 Hz, 1H), 6.35 (d, *J* = 15.3 Hz, 1H), 5.71 (s, 1H), 5.61 (dd, *J* = 10.5 Hz, 15.3 Hz, 1H), 3.32-3.44 (m, 1H), 3.31 (s, 3H), 3.19-3.24 (m, 1H), 2.11 (s, 3H), 1.64-1.85 (m, 1H), 1.64-1.66 (m, 5H), 1.25-1.38 (m, 12H).

(+)-(1S, 2R, 3R)-5-[3-Ethoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoic acid
(**Compound 20b**)

Following a procedure similar to that for the preparation of **Compound 20a** but using **Compound 16b** as the starting material afforded the title compound (36 mg, 91% yield) from 16b as a white solid:

¹HNMR (CDCl₃, 500MHz) δ 7.13 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 1.8 Hz, 1H), 6.90 (dd, *J* = 1.8 Hz, 8.4 Hz, 1H), 6.28 (d, *J* = 15.3 Hz, 1H), 5.64 (s, 1H), 5.50 (dd, *J* = 10.5 Hz, 15.3 Hz, 1H), 3.32-3.38 (m, 3H), 3.16-3.20 (m, 1H), 2.04 (s, 3H), 1.64-1.85 (m, 1H), 1.32-1.59 (m, 5H), 1.31 (s, 3H), 1.25-1.38 (m, 16H).

(-)-(1R, 2S, 3S)-5-[3-Methoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoic acid
(**Compound 21a**)

Following a procedure similar to that for the preparation of **Compound 20a** but using **Compound 17a** as the starting material afforded the title compound (42 mg, 85% yield) as a white solid:

¹HNMR (CDCl₃, 300MHz) δ 7.20 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 1.8 Hz, 1H), 7.04 (dd, *J* = 1.8 Hz, 8.4 Hz, 1H), 6.35 (d, *J* = 15.3 Hz, 1H), 5.71 (s, 1H), 5.61 (dd, *J* = 10.5 Hz, 15.3 Hz, 1H), 3.32-3.44 (m, 1H), 3.31 (s, 3H), 3.19-3.24 (m, 1H), 2.11 (s, 3H), 1.64-1.85 (m, 1H), 1.64-1.66 (m, 5H), 1.25-1.38 (m, 12H).

(-)-(1R, 2S, 3S)-5-[3-Ethoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoic acid
(**Compound 21b**)

Following a procedure similar to that for the preparation of **Compound 20a** but using **Compound 17b** as the starting material afforded the title compound (35 mg, 86% yield) as a white solid:

¹HNMR (CDCl₃, 300MHz) δ 7.13 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 1.8 Hz, 1H), 6.90 (dd, *J* = 1.8 Hz, 8.4 Hz, 1H), 6.28 (d, *J* = 15.3 Hz, 1H), 5.64 (s, 1H), 5.50 (dd, *J* = 10.5 Hz, 15.3 Hz, 1H), 3.32-3.38 (m, 3H), 3.16-3.20 (m, 1H), 2.04 (s, 3H), 1.64-1.85 (m, 1H), 1.32-1.59 (m, 5H), 1.31 (s, 3H), 1.25-1.38 (m, 16H).

(+)-(1S, 2R, 3S)-5-[3-Methoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoic acid
(**Compound 22a**)

Following a procedure similar to that for the preparation of **Compound 20a** but using **Compound 18a** as the starting material afforded the title compound (28 mg, 93% yield) as a white solid:

¹HNMR (CDCl₃, 500MHz) δ 7.20 (d, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 7.00 (dd, *J* = 2.0 Hz, 8.0 Hz, 1H), 6.19 (d, *J* = 15.5 Hz, 1H), 5.63 (s, 1H), 5.30 (dd,

1 $J = 10$ Hz, 15.5 Hz, 1H), 3.62-3.65 (m, 2H), 3.42 (s, 3H), 1.98 (s, 3H), 1.57-1.70
2 (m, 5H), 1.26-1.42 (s, 16H), 1.17 (s, 3H).

3 (+)-(1S, 2R, 3S)-5-[3-Ethoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-
4 tetrahydro-naphthalen-2-yl)-cyclopropyl]-3-methyl-penta-2E,4E-dienoic acid
5 **(Compound 22b)**

6 Following a procedure similar to that for the preparation of **Compound 20a**
7 but using **Compound 18b** as the starting material afforded the title compound (31
8 mg, 87% yield) as a white solid:

9 ^1H NMR (CDCl_3 , 300 MHz) δ 7.20 (d, $J = 8.4$ Hz, 1H), 7.09 (d, $J = 1.8$ Hz, 1H),
10 7.00 (dd, $J = 1.8$ Hz, 8.4 Hz, 1H), 6.20 (d, $J = 15.6$ Hz, 1H), 5.62 (s, 1H), 5.25-5.34
11 (dd, $J = 9.6$ Hz, 15.3 Hz, 1H), 3.52-3.73 (m, 4H), 1.98 (s, 3H), 1.65-1.70 (m, 5H),
12 1.54-1.60 (m, 1H), 1.22-1.41 (m, 18H).

13 (-)-(1R, 2S, 3R)-5-[3-Methoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-
14 tetrahydro-naphthalen-2-yl)-cyclopropyl]-3-methyl-penta-2E,4E-dienoic acid
15 **(Compound 23a)**

16 Following a procedure similar to that for the preparation of **Compound 20a**
17 but using **Compound 19a** as the starting material afforded the title compound (26
18 mg, 80% yield) as a white solid:

19 ^1H NMR (CDCl_3 , 500MHz) δ 7.20 (d, $J = 8.0$ Hz, 1H), 7.09 (d, $J = 2.0$ Hz, 1H),
20 7.00 (dd, $J = 2.0$ Hz, 8.0 Hz, 1H), 6.19 (d, $J = 15.5$ Hz, 1H), 5.63 (s, 1H), 5.30 (dd,
21 $J = 10$ Hz, 15.5 Hz, 1H), 3.62-3.65 (m, 2H), 3.42 (s, 3H), 1.98 (s, 3H), 1.57-1.70
22 (m, 5H), 1.26-1.42 (s, 16H), 1.17 (s, 3H).

1 (-)-(1R, 2S, 3R)-5-[3-Ethoxymethyl-2-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-
 2 tetrahydro-naphthalen-2-yl)-cyclopropyl]-3-methyl-penta-2E,4E-dienoic acid
 3 **(Compound 23b)**

4 Following a procedure similar to that for the preparation of **Compound 20a**
 5 but using **Compound 19b** as the starting material afforded the title compound (26
 6 mg, 80% yield) as a white solid:

7 ¹HNMR (CDCl₃, 500MHz) δ 7.20 (d, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 1.8 Hz, 1H),
 8 7.00 (dd, *J* = 1.8 Hz, 8.4 Hz, 1H), 6.20 (d, *J* = 15.6 Hz, 1H), 5.62 (s, 1H), 5.25-5.34
 9 (dd, *J* = 9.6 Hz, 15.3 Hz, 1H), 3.52-3.73 (m, 4H), 1.98 (s, 3H), 1.65-1.70 (m, 5H),
 10 1.54-1.60 (m, 1H), 1.22-1.41 (m, 18H).

11 2,4-Diisopropyl-1-nitro-benzene (Intermediate 32)

12 Nitric acid (70%) (15.6 g, 185 mmol) was added slowly to a solution of 1,3-
 13 di-iso-propyl-benzene (available from Aldrich) (20 g, 123 mmol) in acetic acid
 14 (50 mL) and acetic anhydride (50 mL) at 0° C over 20 min. After stirring at room
 15 temperature for 1 hour, the reaction mixture was diluted with water (250 mL) and
 16 hexane (500 mL). The organic layer was then washed with with water (50 mL),
 17 saturated Na₂CO₃ (50 mL), dried (Na₂SO₄) and concentrated to give the title
 18 compound in a crude form (25 g, 98% yield) as a colorless oil:

19 ¹HNMR (CDCl₃, 300MHz) δ 7.69 (d, *J* = 2.1 Hz, 1H), 7.28 (d, *J* = 2.1 Hz, 1H),
 20 7.14 (dd, *J* = 2.1 Hz, 8.4 Hz, 1H), 3.50 (m, 1H), 2.9 (m, 1H), 1.25 (m, 12H).

21 2,4-Diisopropyl-1-amino-benzene (Intermediate 33)

22 Mossey Tin (22 g, 184.5 mmol) was added to a solution of **Intermediate 32**
 23 (25 g, 120 mmol), followed by conc. HCl (150 mL). After heating at 100° C for 1

hour, acetic acid (50 mL) was added to the mixture and it was heated for another 30 minutes. After stirring at room temperature overnight, the reaction mixture was diluted with ether (500 mL), washed with water (50 mL) and transferred to a 500 mL beaker. Solid potassium carbonate was carefully added until all acids were quenched (~80 g). The mixture was then extracted with ether (3 x 100 mL), washed with brine (1 x 20 mL), dried (Na_2SO_4) and concentrated to give the title compound in a crude form as a brown oil that was taken to the next step without further purification :

^1H NMR (CDCl_3 , 300MHz) δ 7.01 (d, $J = 2.1$ Hz, 1H), 6.91 (dd, $J = 2.1$ Hz, 8.1 Hz, 1H), 6.60 (d, $J = 8.1$ Hz, 1H), 5.80 (bs, 2H), 2.80-2.94 (m, 2H), 1.28-1.20 (m, 12H).

2,6-Diisopropyl-1-amino-2-bromo-benzene (Intermediate 34)

Bromine (19.7 mL, 123 mmol) was added to a solution of **Intermediate 33** (crude) in acetic acid (100 mL) at 0°C *via* addition funnel. After stirring at room temperature for 1 hour, the reaction mixture was diluted with water (200 mL) and diethyl ether (500 mL). The organic layer was then isolated and washed with water (50 mL). Solid potassium carbonate was carefully added to neutralize the solution. The ether layer was separated and washed with brine, dried (Na_2SO_4) and concentrated to give **Intermediate 34** as a brown oil which was taken to the next step without further purification :

^1H NMR (CDCl_3 , 300MHz) δ 7.16 (d, $J = 2.1$ Hz, 1H), 6.93 (d, $J = 1.8$ Hz, 1H), 2.75-2.90 (m, 2H), 1.18-1.26 (m, 12H).

2,5-Diisopropyl-1-bromo-benzene (Intermediate 35)

Trifluoroacetic acid (75 mL) was added to a solution of **Intermediate 34** in EtOH (100 mL) at 0° C. After stirring for 10 min, *iso*-amyl nitrite (100 mL) was then added and the mixture was stirred for another 70 min. H₃PO₂ (70 mL) was added slowly and the mixture was warmed to ambient temperature over 5 hours. After dilution with ethyl acetate and sodium bicarbonate solution, the organic layer was separated, dried and concentrated to give the title compound in a crude form (17 g). Purification of the crude product by Kugelrohr distillation gave the title compound in pure form (13 g, 44 % yield over 4 steps from 1,3-di-*iso*-propylbenzene) as a colorless oil:

¹H NMR (CDCl₃, 300 MHz) δ 7.18 (d, *J* = 1.5 Hz, 2H), 6.99 (s, 1H), 2.80-2.87 (m, 2H), 1.24 (s, 6H), 1.22 (s, 6H).

tert-Butyl-[3-(3,5-diisopropyl-phenyl)-but-2-enyloxy]-dimethyl-silane
(**Intermediate 36**)

Bis(pinacolato)diboron (5.6 g, 22 mmol), potassium acetate (4.4 g, 44 mmol) and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium (PdCl₂(dppf)₂) (730 mg, 0.89 mmol) were added to a solution of **Intermediate 35** (3.5 g, 14.6 mmol) in 50 mL of DMF under argon. The mixture was then stirred at 80° C for 24 h. After cooling to room temperature, 3-iodo-but-2*Z*-en-1-ol (obtainable in accordance with United States Patent No. 6,147,224) (5.8 g, 29.2 mmol), 2M Na₂CO₃ (30 mL), and PdCl₂(dppf)₂ (730 mg, 0.89 mmol) were added to the mixture, which was then stirred at 80° C for another 24 h. The reaction was finally quenched with water (20 mL) and extracted with diethyl ether (3 x 10 mL). The organic layer was washed with brine (2 x 10 mL), dried (MgSO₄) and concentrated

to give a crude brown oil. The crude oil was purified by flash chromatography using 20% EtOAc in hexane to obtain allylic alcohol (3 g, 88% yield) as a colorless oil.

tert-Butyldimethylsilyl chloride (3.9 g, 25.9 mmol) was added to the solution of allylic alcohol, (3 g, 12.9 mmol) and imidazole (2.6 g, 38.7 mmol) in 10 mL of DMF. The mixture was then stirred for 16 h at room temperature. After quenching with water, the mixture was extracted with diethyl ether (3 x 10 mL), washed with brine (1 x 10 mL), dried (MgSO₄) and concentrated to give a crude brown oil. The crude oil was purified by flash chromatography using 10% EtOAc in hexane to give the title compound (3.6 g, 80% yield) as a colorless oil:

¹H NMR (CDCl₃, 300 MHz) δ 6.98 (d, J = 1.2 Hz, 1H), 6.86 (d, J = 1.8 Hz, 2H), 5.65 (t, J = 6.9 Hz, 1H), 4.14 (d, J = 6.9 Hz, 2H), 2.84-2.94 (m, 2H), 1.29 (s, 3H), 1.27 (s, 6H), 1.25 (s, 6H), 0.86 (s, 9H), 0.00 (s, 6H).

(\pm)-[(R)-3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-(3,5-diisopropyl-phenyl)-2-methyl-cyclopropyl]-methanol (**Intermediate 37**) and (\pm)-[(S)-3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-(3,5-diisopropyl-phenyl)-2-methyl-cyclopropyl]-methanol (**Intermediate 38**)

Ethyl diazoacetate (5 mL, 48 mmol) in 10 mL of benzene was added slowly with a syringe pump (2 mL/h) to a solution of **Intermediate 36** (0.7 g, 2 mmol) and anhydrous copper (II) sulfate (60 mg, 376 μ mol) in 30 mL of benzene (30 mL) at 80° C. After completion of the addition of ethyl diazoacetate, the mixture was allowed to stir for 16 h at room temperature in order to decompose the excess of ethyl diazoacetate. The solvent was then evaporated under reduced pressure and

1 the residue was purified by flash chromatography using 2% EtOAc in hexane to
 2 yield 1.2 g of a mixture of crude cyclopropyl esters, which was then dissolved in
 3 15 mL of anhydrous THF and cooled to -78°C with a dry ice/acetone bath. To this
 4 solution was added di-*iso*-butyl aluminum hydride (DIBAL-H) in hexane (1M, 10
 5 mL, 10 mmol). After stirring at -78°C for 2 h, the reaction was quenched with
 6 saturated NH_4Cl (2 mL). Celite (2 g) and diethyl ether (50 mL) were then added to
 7 the mixture and stirring was continued at 0°C until all aluminum salt precipitated
 8 out. Inorganic material was removed by filtration, and solvents were removed
 9 under reduced pressure to give a brown oil, which was purified by flash
 10 chromatography using 20% EtOAc in hexane to obtain **Intermediate 37** (154 mg,
 11 20% yield) and **Intermediate 38** (160 mg, 21% yield) as colorless oil:

12 ^1H NMR for **Intermediate 37**: (CDCl_3 , 300MHz) δ 6.84 (s, 1H), 6.64 (s, 2H), 4.09
 13 (dd, $J = 5.4\text{ Hz}, 11.7\text{ Hz}$, 1H), 3.90-3.92 (m, 1H), 3.14 (q, $J = 11.1\text{ Hz}$, 2H), 2.75-
 14 2.82 (m, 2H), 1.40-1.48 (m, 2H), 1.26 (s, 3H), 1.18 (s, 6H), 1.15 (s, 6H), 0.82 (s,
 15 9H), 0.17 (d, $J = 15.6\text{ Hz}$, 6H);

16 ^1H NMR for **Intermediate 38**: (CDCl_3 , 300MHz) δ 7.00 (s, 2H), 6.96 (s, 1H), 3.85-
 17 3.89 (m, 2H), 3.47-3.53 (m, 1H), 3.06-3.13 (m, 1H), 2.86-2.95 (m, 2H), 1.42 (s,
 18 3H), 1.07-1.13 (m, 1H), 0.97-0.93 (m, 1H), 0.90 (s, 9H), 0.00 (d, $J = 2.1\text{ Hz}$, 6H).

19 (\pm)-[(R)-3-Methoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-cyclopropyl]-
 20 methanol (Intermediate 39)

21 Sodium hydride (40 mg, 1.52 mmol) was added slowly to a solution of
 22 **Intermediate 37** (50 mg, 0.38 mmol) in 5 mL of DMF at 0°C . After stirring for
 23 10 min, methyl iodide (0.100 mL, 1.52 mmol) was added to the mixture, which

was then stirred at room temperature for 16 h. The reaction was quenched with saturated NH_4Cl , extracted with diethyl ether (3 x 10 mL), washed with brine (1 x 10 mL), dried (Na_2SO_4) and concentrated to give a crude brown oil. Purification by flash chromatography using 5% EtOAc in hexane afforded the methylated intermediate (136 mg, 87% yield) as a colorless oil, which was then dissolved in 5 mL of anhydrous THF and cooled to 0° C with an ice bath. To this solution was added TBAF in THF (1M, 0.5 mL, 0.5 mmol) and the reaction mixture was allowed to stir at room temperature for 2 h. The reaction was finally quenched with water, extracted with ether (3 x 10 mL), washed with brine (1 x 10 mL), dried (Na_2SO_4) and concentrated to give a crude colorless oil. Purification by flash chromatography using 20% EtOAc in hexane gave **Intermediate 39** (100 mg, 100% yield) as a colorless oil:

^1H NMR (CDCl_3 , 300MHz) δ 6.91 (s, 1H), 6.72 (s, 2H), 3.98 (dd, J = 4.5 Hz, 12 Hz, 1H), 3.78 (dd, J = 5.4 Hz, 10.2 Hz, 1H), 3.31 (s, 3H), 2.96-3.14 (m, 2H), 2.79-2.88 (m, 2H), 1.40-1.50 (m, 2H), 1.33 (s, 3H), 1.24 (s, 6H), 1.21 (s, 6H).

(\pm)-[(S)- 3-Methoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-cyclopropyl]-methanol (**Intermediate 40a**)

Following a procedure similar to that for the preparation of **Intermediate 39** but using **Intermediate 38** as the starting material yielded the title compound (35 mg, 48% yield) as a colorless oil:

^1H NMR (CDCl_3 , 300MHz) δ 7.00 (d, J = 1.8 Hz, 1H), 6.96 (s, 1H), 3.55-3.65 (m, 2H), 3.42 (s, 3H), 3.30-3.40 (m, 1H), 3.18-3.22 (m, 1H), 1.80-2.15 (m, 2H), 1.40 (s, 3H), 1.25 (s, 6H), 1.22 (s, 6H).

1 (±)-[(S)-3-Ethoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-cyclopropyl]-
 2 methanol (Intermediate 40b)

3 Following a procedure similar to that for the preparation of **Intermediate 39**
 4 but using **Intermediate 38** as the starting material and ethyl iodide as alkylating
 5 reagent yielded the title compound (89 mg, 77% yield) as a colorless oil:

6 ¹HNMR (CDCl₃, 300MHz) δ. 6.88 (d, *J* = 1.8 Hz, 2H), 6.82 (d, *J* = 1.5 Hz, 1H),
 7 3.45-3.85 (m, 4H), 3.24-3.30 (m, 1H), 3.05-3.08 (m, 1H), 2.72-2.81 (m, 2H), 1.25-
 8 1.38 (m, 4H), 1.15 (s, 6H), 1.13 (s, 6H), 1.00-1.12 (m, 1H).

9 (1S, 2R, 3R)-3-Methoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-
 10 cyclopropylmethyl 4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-
 11 carboxylate (Intermediate 41) and (1R, 2S, 3S)-3-Methoxymethyl-2-methyl-2-
 12 (3,5-diisopropyl-phenyl)-cyclopropylmethyl 4,7,7-trimethyl-3-oxo-2-oxa-
 13 bicyclo[2.2.1]heptane-1-carboxylate (Intermediate 42)

14 1-(S)-(-)-Camphanic chloride (118 mg, 0.55 mmol) and *N,N*-
 15 dimethylaminopyridine (80 mg, 0.66 mmol) were added to a solution of
 16 **Intermediate 39** (100 mg, 0.34 mmol) in 5 mL of dichloromethane. After stirring
 17 at room temperature for 16 h, the mixture was extracted with dichloromethane (2 x
 18 10 mL), washed with water (1 x 10 mL), dried (Na₂SO₄) and concentrated to give a
 19 crude colorless oil. Purification by column chromatography using 10% EtOAc in
 20 hexane afforded a mixture of the title compounds in 1:1 ratio (150 mg, 94% yield).
 21 Separation of this mixture with normal phase HPLC (Whatman, Partisil-10-PAC
 22 HPLC column) using 8% EtOAc in hexane as eluent provided **Intermediate 41**
 23 (60 mg, 38% yield) and **Intermediate 42** (59 mg, 38% yield) as colorless oils :

¹HNMR for **Intermediate 41**: (CDCl₃, 300MHz) δ 6.98 (s, 2H), 6.94 (s, 1H), 4.30-4.36 (m, 1H), 3.91-3.97 (m, 1H), 3.18-3.36 (m, 5H), 2.80-2.89 (m, 1H), 2.41-2.50 (m, 1H), 1.88-2.09 (m, 2H), 1.63-1.74 (m, 1H), 1.28-1.44 (m, 5H), 1.24 (s, 6H), 1.22 (s, 6H), 1.12 (s, 3H), 1.08 (s, 3H), 0.98 (s, 3H);

¹HNMR for **Intermediate 42**: (CDCl₃, 300MHz) δ 6.99 (s, 2H), 6.93 (s, 1H), 4.26-4.32 (m, 1H), 3.92-3.99 (m, 1H), 3.20-3.33 (m, 5H), 2.80-2.90 (m, 2H), 2.39-2.48 (m, 1H), 1.87-2.07 (m, 2H), 1.55-1.74 (m, 1H), 1.39-1.46 (m, 5H), 1.37 (s, 3H), 1.25 (s, 6H), 1.22 (s, 3H), 1.12 (s, 3H), 1.06 (s, 3H), 0.99 (s, 3H).

(1S, 2R, 3S)-3-Methoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-cyclopropylmethyl 4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylate (Intermediate 43a) and (1R, 2S, 3R)-3-Methoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-cyclopropylmethyl 4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylate (Intermediate 44a)

Following a procedure similar to that for the preparation of **Intermediates 41** and **42** but using **Intermediate 40a** as the starting material and using 10% EtOAc in hexane as normal phase HPLC eluent afforded **Intermediate 43a** (25 mg, 45% yield) and **Intermediate 44a** (23 mg, 41% yield) as colorless oils :

¹HNMR for **Intermediate 43a**: (CDCl₃, 300MHz) δ 6.93 (s, 3H), 3.98-4.05 (m, 1H), 3.74-3.81 (m, 1H), 3.41-3.63 (m, 2H), 3.40 (s, 3H), 2.79-2.89 (m, 2H), 2.37-2.45 (m, 1H), 1.91-2.05 (m, 2H), 1.62-1.72 (m, 1H), 1.50-1.54 (m, 1H), 1.39 (s, 3H), 1.23 (s, 6H), 1.21 (s, 6H), 1.10 (s, 3H), 1.05 (s, 3H), 0.94 (s, 3H);

¹HNMR for **Intermediate 44a**: (CDCl₃, 300MHz) δ 6.94 (s, 2H), 6.92 (s, 1H), 3.95-4.01 (m, 1H), 3.76-3.82 (m, 1H), 3.50-3.63 (m, 4H), 3.41 (s, 3H), 2.80-2.89

1 (m, 2H), 2.33-2.43 (m, 1H), 1.85-2.02 (m, 2H), 1.63-1.72 (m, 1H), 1.46-1.53 (m,
2 1H), 1.39 (s, 3H), 1.24 (s, 6H), 1.21 (s, 6H), 1.11 (s, 3H), 1.04 (s, 3H), 0.97 (s,
3 3H).

4 (1S, 2R, 3S)-3-Ethoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-
5 cyclopropylmethyl 4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-
6 carboxylate (Intermediate 43b) and (1R, 2S, 3R)-3-Ethoxymethyl-2-methyl-2-
7 (3,5-diisopropyl-phenyl)-cyclopropylmethyl 4,7,7-trimethyl-3-oxo-2-oxa-
8 bicyclo[2.2.1]heptane-1-carboxylate (Intermediate 44b)

9 Following a procedure similar to that for the preparation of **Intermediates**
10 **41** and **42** but using **Intermediate 40b** as the starting material, ethyl iodide as the
11 alkylating reagent and using 10% EtOAc in hexane as normal phase HPLC eluent
12 afforded **Intermediate 43b** (59 mg, 43% yield) and **Intermediate 44b** (56 mg,
13 41% yield) as colorless oils:

14 ¹HNMR for **Intermediate 43b**: (CDCl₃, 300MHz) δ 6.93 (d, *J* = 1.5 Hz, 2H), 6.92
15 (d, *J* = 1.2 Hz, 1H), 3.99-4.05 (m, 1H), 3.74-3.81 (m, 1H), 3.52-3.63 (m, 4H), 2.80-
16 2.89 (m, 2H), 2.37-2.46 (m, 1H), 1.86-2.05 (m, 2H), 1.62-1.72 (m, 1H), 1.47-1.56
17 (m, 1H), 1.39 (s, 3H), 1.23 (s, 6H), 1.21 (s, 6H), 1.10 (s, 3H), 1.05 (s, 3H), 0.94 (s,
18 3H);

19 ¹HNMR for **Intermediate 44b**: (CDCl₃, 300MHz) δ 6.94 (s, 2H), 6.91 (s, 1H),
20 3.94-4.00 (m, 1H), 3.76-3.84 (m, 1H), 3.55-3.62 (m, 4H), 2.82-2.89 (m, 2H), 2.35-
21 2.38 (m, 1H), 1.86-2.03 (m, 2H), 1.67-1.70 (m, 1H), 1.56 (s, 3H), 1.48-1.52 (m,
22 1H), 1.38 (s, 3H), 1.24 (s, 6H), 1.21 (s, 6H), 1.21 (s, 6H), 1.11 (s, 3H), 1.04 (s, 3H),
23 0.97 (s, 3H).

1 (+)-(1S, 2R, 3R)-3-Methoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-
2 cyclopropanecarbaldehyde (Intermediate 45)

3 Potassium hydroxide solution (1N, 1 mL) was added to a solution of
4 **Intermediate 41** (26 mg, 0.056 mmol) in 4 mL of THF/MeOH (1: 1) at room
5 temperature. After stirring for an hour, the mixture was diluted with ethyl acetate
6 (10 mL) and acidified with 1 mL of 1 N HCl at 0° C. The organic layer was then
7 washed with brine (1 x 5 mL), dried (Na₂SO₄) and concentrated. The residue was
8 purified by flash chromatography using 20% EtOAc in hexane to give the
9 corresponding alcohol (16 mg, 100% yield). This alcohol was subsequently
10 dissolved in dichloromethane (5 mL) and acetonitrile (0.5 mL). To this solution
11 was added molecular sieve (45 mg), 4-methylmorpholine *N*-oxide (23 mg, 0.40
12 mmol) and tetrapropylammonium perruthenate (5 mg, 0.01 mmol). After stirring at
13 room temperature for 45 min, the solvent was then removed under reduced
14 pressure and the residue was purified by flash chromatography using 10% EtOAc
15 in hexane to obtain the title compound in optically pure form (15 mg, 99% yield)
16 as a colorless oil:

17 ¹HNMR (CDCl₃, 300MHz) δ 8.8 (d, *J* = 7.5 Hz, 1H), 7.15-7.18 (m, 2H), 6.90 (dd,
18 *J* = 4 Hz, 14 Hz, 1H), 3.62-3.68 (m, 1H), 3.26-3.41 (m, 1H), 3.26 (s, 3H), 1.88-
19 1.97 (m, 2H), 1.60 (s, 4H), 1.35 (s, 3H), 1.19 (s, 12H).

20 (-)-(1R, 2S, 3S)-3-Methoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-
21 cyclopropanecarbaldehyde (Intermediate 46)

Following a procedure similar to that for the preparation of **Intermediate 45** but using **Intermediate 42** as the starting material afforded the title compound (14 mg, 92% yield) as a colorless oil:

¹HNMR (CDCl₃, 300MHz) δ 8.8 (d, *J* = 7.5 Hz, 1H), 7.15-7.18 (m, 2H), 6.90 (dd, *J* = 4 Hz, 14 Hz, 1H), 3.62-3.68 (m, 1H), 3.26-3.41 (m, 1H), 3.26 (s, 3H), 1.88-1.97 (m, 2H), 1.60 (s, 4H), 1.35 (s, 3H), 1.19 (s, 12H).

(+)-(1S, 2R, 3S)-3-Methoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-cyclopropanecarbaldehyde (Intermediate 47a)

Following a procedure similar to that for the preparation of **Intermediate 45** but using **Intermediate 43a** as the starting material afforded the title compound (16 mg, 95% yield) as a colorless oil:

¹HNMR (CDCl₃, 300MHz) δ 8.37 (d, *J* = 6.9 Hz, 1H), 6.90 (d, *J* = 1.5 Hz, 2H), 6.88 (d, *J* = 1.2 Hz, 1H), 3.60-3.65 (m, 1H), 3.47-3.53 (m, 1H), 3.37 (s, 3H), 2.83-2.74 (m, 2H), 2.32-2.39 (m, 1H), 1.68-1.72 (m, 1H), 1.40 (s, 3H), 1.16 (s, 6H), 1.14 (s, 6H).

(+)-(1S, 2R, 3S)-3-Ethoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-cyclopropanecarbaldehyde (Intermediate 47b)

Following a procedure similar to that for the preparation of **Intermediate 45** but using **Intermediate 43b** as the starting material afforded the title compound (30 mg, 83% yield) as a colorless oil:

¹HNMR (CDCl₃, 300MHz) δ 8.42 (d, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 1.5 Hz, 2H), 6.94 (d, *J* = 1.2 Hz, 1H), 3.54-3.73 (m, 4H), 2.80-2.90 (m, 2H), 2.39-2.45 (m, 1H), 1.75-1.79 (m, 1H), 1.46 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.23 (s, 6H), 1.21 (s, 6H).

1 (-)-(1R, 2S, 3R)-3-Methoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-
 2 cyclopropanecarbaldehyde (Intermediate 48a)

3 Following a procedure similar to that for the preparation of **Intermediate 45**
 4 but using **Intermediate 44a** as the starting material afforded the title compound
 5 (14 mg, 87% yield) as a colorless oil:

6 ¹HNMR (CDCl₃, 300MHz) δ 8.37 (d, *J* = 6.9 Hz, 1H), 6.90 (d, *J* = 1.5 Hz, 2H),
 7 6.88 (d, *J* = 1.2 Hz, 1H), 3.60-3.65 (m, 1H), 3.47-3.53 (m, 1H), 3.37 (s, 3H), 2.83-
 8 2.74 (m, 2H), 2.32-2.39 (m, 1H), 1.68-1.72 (m, 1H), 1.40 (s, 3H), 1.16 (s, 6H),
 9 1.14 (s, 6H).

10 (-)-(1R, 2S, 3R)-3-Ethoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-
 11 cyclopropanecarbaldehyde (Intermediate 48b)

12 Following a procedure similar to that for the preparation of **Intermediate 45**
 13 but using **Intermediate 44b** as the starting material afforded the title compound
 14 (39 mg, 98% yield) as a colorless oil:

15 ¹HNMR (CDCl₃, 300MHz) δ 8.42 (d, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 1.5 Hz, 2H),
 16 6.94 (d, *J* = 1.2 Hz, 1H), 3.54-3.73 (m, 4H), 2.80-2.90 (m, 2H), 2.39-2.45 (m, 1H),
 17 1.75-1.79 (m, 1H), 1.46 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.23 (s, 6H), 1.21 (s, 6H).

18 Ethyl (+)-(1S, 2R, 3R)-5-[3-methoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-
 19 cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoate (Compound 24)

20 *n*-Butyl lithium in hexane (1.6 M, 0.56 mL, 0.89 mmol) was added to a
 21 solution of triethylphosphono-3-methyl-2*E*-butenoate (264 mg, 1.0 mmol) in 5 mL
 22 of THF and 3 mL of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU)
 23 at -78° C. After stirring for 5 min, a solution of **Intermediate 45** (15 mg, 0.20

mmol) in 1 mL of THF was added by cannulation. The resulting solution was stirred at -78 °C for 2h and then quenched with saturated NH₄Cl. The mixture was then extracted with diethyl ether (3 x 5 mL), washed with brine (1 x 10 mL), dried (Na₂SO₄) and concentrated to give a crude colorless oil. Purification by column chromatography using 5% EtOAc in hexane afforded the title compound (20 mg, 85% yield) as a white solid:

¹HNMR (CDCl₃, 300MHz) δ 6.87 (s, 3H), 6.24 (d, *J* = 15.6 Hz, 1H), 5.62 (s, 1H), 5.44 (dd, *J* = 10.5Hz, 15.3 Hz, 1H), 4.07 (q, *J* = 6.9 Hz, 2H), 3.15 -3.26 (m, 5H), 2.73-2.85 (m, 2H), 2.03 (s, 3H), 1.71-1.81 (m, 1H), 1.50-1.58 (m, 1H), 1.33 (s, 3H), 1.14-1.25 (m, 15H).

Ethyl (-)-(1R, 2S, 3S)-5-[3-methoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoate (Compound 25)

Following a procedure similar to that for the preparation of **Compound 24** but using **Intermediate 46** as the starting material afforded the title compound (15 mg, 76% yield) as a white solid:

¹HNMR (CDCl₃, 300MHz) δ 6.87 (s, 3H), 6.24 (d, *J* = 15.6 Hz, 1H), 5.62 (s, 1H), 5.44 (dd, *J* = 10.5Hz, 15.3 Hz, 1H), 4.07 (q, *J* = 6.9 Hz, 2H), 3.15-3.26 (m, 5H), 2.73-2.85 (m, 2H), 2.03 (s, 3H), 1.71-1.81 (m, 1H), 1.50-1.58 (m, 1H), 1.33 (s, 3H), 1.14-1.25 (m, 15H).

Ethyl (+)-(1S, 2R, 3S)-5-[3-methoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoate (Compound 26a)

Following a procedure similar to that for the preparation of **Compound 24** but using **Intermediate 47a** as the starting material afforded the title compound (19 mg, 85 % yield) as a white solid:

¹HNMR (CDCl₃, 300MHz) δ 6.83 (d, *J* = 1.5 Hz, 1H), 6.82 (d, *J* = 1.5 Hz, 2H), 6.10 (d, *J* = 15.5 Hz, 1H), 5.55 (s, 1H), 5.18 (dd, *J* = 10 Hz, 16 Hz, 1H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.53-3.60 (m, 2H), 3.36 (s, 3H), 2.74-2.80 (m, 2H), 1.92 (s, 3H), 1.60-1.62 (m, 1H), 1.50-1.59 (m, 1H), 1.36 (s, 3H), 1.21 (t, *J* = 7.5 Hz, 3H), 1.15 (s, 6H), 1.13 (s, 6H).

Ethyl (+)-(1S, 2R, 3S)-5-[3-ethoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoate (Compound 26b)

Following a procedure similar to that for the preparation of **Compound 24** but using **Intermediate 47b** as the starting material afforded the title compound (37 mg, 90% yield) as a white solid:

¹HNMR (CDCl₃, 300MHz) δ 6.83 (s, 3H), 6.10 (d, *J* = 15.3 Hz, 1H), 5.55 (s, 1H), 5.18 (dd, *J* = 10 Hz, 16 Hz, 1H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.61 (d, *J* = 6.9 Hz, 2H), 3.45-3.59 (m, 2H), 2.73-2.82 (m, 2H), 1.92 (s, 3H), 1.60-1.62 (m, 1H), 1.50-1.59 (m, 1H), 1.36 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 1.15 (s, 6H), 1.13 (s, 6H).

Ethyl (-)-(1R, 2S, 3R)-5-[3-methoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoate (Compound 27a)

Following a procedure similar to that for the preparation of **Compound 24** but using **Intermediate 48a** as the starting material afforded the title compound (14 mg, 73% yield) as a white solid:

¹HNMR (CDCl₃, 300MHz) δ 6.83 (d, *J* = 1.5 Hz, 1H), 6.82 (d, *J* = 1.5 Hz, 2H), 6.10 (d, *J* = 15.5 Hz, 1H), 5.55 (s, 1H), 5.18 (dd, *J* = 10 Hz, 16 Hz, 1H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.53-3.60 (m, 2H), 3.36 (s, 3H), 2.74-2.80 (m, 2H), 1.92 (s, 3H), 1.60-1.62 (m, 1H), 1.50-1.59 (m, 1H), 1.36 (s, 3H), 1.21 (t, *J* = 7.5 Hz, 3H), 1.15 (s, 6H), 1.13 (s, 6H).

Ethyl (-)-(1R, 2S, 3R)-5-[3-ethoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoate (Compound 27b)

Following a procedure similar to that for the preparation of **Compound 24** but using **Intermediate 48b** as the starting material afforded the title compound (36 mg, 73% yield) as a white solid:

¹HNMR (CDCl₃, 300MHz) δ 6.83 (s, 3H), 6.10 (d, *J* = 15.3 Hz, 1H), 5.55 (s, 1H), 5.18 (dd, *J* = 10 Hz, 16 Hz, 1H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.61 (d, *J* = 6.9 Hz, 2H), 3.45-3.59 (m, 2H), 2.73-2.82 (m, 2H), 1.92 (s, 3H), 1.60-1.62 (m, 1H), 1.50-1.59 (m, 1H), 1.36 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 1.15 (s, 6H), 1.13 (s, 6H).

(+)-(1S, 2R, 3R)-5-[3-Methoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoic acid (Compound 28)

Sodium hydroxide solution (1N, 1mL) was added to a solution of **Compound 24** (20 mg, 0.05 mmol) in 4 mL of THF/MeOH (1 :1) at 50° C. After stirring at 50° C for 16 h, the mixture was diluted with ethyl acetate (10 mL) and acidified with 1 mL of 1 HCl at 0° C. The organic layer was then washed with brine (1 x 5 mL), dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography using 30% EtOAc in hexane to give the title compound (17 mg, 91% yield) as a white solid:

¹HNMR (CDCl₃, 300MHz) δ 6.94 (s, 3H), 6.35 (d, *J* = 15.6 Hz, 1H), 5.71 (s, 1H), 5.66 (dd, *J* = 10.5 Hz, 15.3 Hz, 1H), 3.23-3.32 (m, 5H), 2.80-2.88 (m, 2H), 2.10 (s, 3H), 1.82-1.92 (m, 1H), 1.63-1.65 (m, 1H), 1.41 (s, 3H), 1.24 (s, 6H), 1.21 (s, 6H).

(-)-(1R, 2S, 3S)-5-[3-Methoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoic acid (Compound 29)

Following a procedure similar to that for the preparation of **Compound 28** but using **Compound 25** as the starting material afforded the title compound (10 mg, 73% yield) as a white solid:

¹HNMR (CDCl₃, 300MHz) δ 6.94 (s, 3H), 6.35 (d, *J* = 15.6 Hz, 1H), 5.71 (s, 1H), 5.66 (dd, *J* = 10.5 Hz, 15.3 Hz, 1H), 3.23-3.32 (m, 5H), 2.80-2.88 (m, 2H), 2.10 (s, 3H), 1.82-1.92 (m, 1H), 1.63-1.65 (m, 1H), 1.41 (s, 3H), 1.24 (s, 6H), 1.21 (s, 6H).

(+)-(1S, 2R, 3S)-5-[3-Methoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoic acid (Compound 30a)

Following a procedure similar to that for the preparation of **Compound 28** but using **Compound 26a** as the starting material afforded the title compound (8 mg, 47% yield) as a white solid:

¹HNMR (CDCl₃, 300MHz) δ 6.83 (d, *J* = 1.5 Hz, 1H), 6.82 (d, *J* = 1.5 Hz, 2H), 6.12 (d, *J* = 15.6 Hz, 1H), 5.57 (s, 1H), 5.26 (dd, *J* = 9.6 Hz, 15.6 Hz, 1H), 3.58 (d, *J* = 7.2 Hz, 2H), 3.36 (s, 3H), 2.73-2.82 (m, 2H), 1.92 (s, 3H), 1.60-1.66 (m, 1H), 1.49-1.52 (m, 1H), 1.36 (s, 3H), 1.15 (s, 6H), 1.13 (s, 6H).

(+)-(1S, 2R, 3S)-5-[3-Ethoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoic acid (Compound 30b)

Following a procedure similar to that for the preparation of **Compound 28** but using **Compound 26b** as the starting material afforded the title compound (29 mg, 84% yield) as a white solid:

¹HNMR (CDCl₃, 300 MHz) δ 6.90 (d, *J* = 1.5 Hz, 1H), 6.89 (d, *J* = 1.5 Hz, 2H), 6.18 (d, *J* = 15.5 Hz, 1H), 5.63 (s, 1H), 5.29 (dd, *J* = 9.6 Hz, 15.6 Hz, 1H), 3.65-3.73 (m, 2H), 3.54-3.63 (m, 2H), 2.81-2.87 (m, 2H), 1.98 (s, 3H), 1.70-1.72 (m, 1H), 1.57-1.68 (m, 1H), 1.43 (s, 3H), 1.28 (t, *J* = 7 Hz, 3H), 1.22 (m, 6H), 1.20 (s, 6H).

(-)-(1R, 2S, 3R)-5-[3-Methoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoic acid (Compound 31a)

Following a procedure similar to that for the preparation of **Compound 28** but using **Compound 27a** as the starting material afforded the title compound (9 mg, 70% yield) as a white solid:

¹HNMR (CDCl₃, 300MHz) δ 6.83 (d, *J* = 1.5 Hz, 1H), 6.82 (d, *J* = 1.5 Hz, 2H), 6.12 (d, *J* = 15.6 Hz, 1H), 5.57 (s, 1H), 5.26 (dd, *J* = 9.6 Hz, 15.6 Hz, 1H), 3.58 (d, *J* = 7.2 Hz, 2H), 3.36 (s, 3H), 2.73-2.82 (m, 2H), 1.92 (s, 3H), 1.60-1.66 (m, 1H), 1.49-1.52 (m, 1H), 1.36 (s, 3H), 1.15 (s, 6H), 1.13 (s, 6H).

(-)-(1R, 2S, 3R)-5-[3-Ethoxymethyl-2-methyl-2-(3,5-diisopropyl-phenyl)-cyclopropyl]-3-methyl-penta-2*E*,4*E*-dienoic acid (Compound 31b)

Following a procedure similar to that for the preparation of **Compound 28** but using **Compound 27b** as the starting material afforded the title compound (28 mg, 85% yield) as a white solid:

1 ^1H NMR (CDCl_3 , 300 MHz) δ 6.90 (d, $J = 1.5$ Hz, 1H), 6.89 (d, $J = 1.5$ Hz, 2H),
2 6.18 (d, $J = 15.5$ Hz, 1H), 5.63 (s, 1H), 5.29 (dd, $J = 9.6$ Hz, 15.6 Hz, 1H), 3.65-
3 3.73 (m, 2H), 3.54-3.63 (m, 2H), 2.81-2.87 (m, 2H), 1.98 (s, 3H), 1.70-1.72 (m,
4 1H), 1.57-1.68 (m, 1H), 1.43 (s, 3H), 1.28 (t, $J = 7$ Hz, 3H), 1.22 (m, 6H), 1.20 (s,
5 6H).
6

BIOLOGICAL ACTIVITY, MODES OF ADMINISTRATION

It has been discovered in accordance with the present invention that compounds of this invention are capable of significantly reducing serum glucose levels and reducing or maintaining serum triglyceride levels in diabetic mammals, without the undesirable side effects of reducing serum thyroxine levels (hypothyroidism) and transiently raising triglyceride levels (hypertriglyceridemia). The compounds of the invention were tested in certain assays for activity as agonists of RAR and RXR retinoid receptors. These assays demonstrated that the compounds of the invention are partial agonists of the RXR receptors.

Specifically, one such assay is a **chimeric receptor transactivation assay** which tests for agonist-like activity in the RAR $_{\alpha}$, RAR $_{\beta}$ and RAR $_{\gamma}$ receptor subtypes, and which is based on work published by *Feigner P. L. and Holm M.* (1989) Focus, 112 is described in detail in United States Patent No. 5,455,265. The specification of United States Patent No. 5,455,265 is hereby expressly incorporated by reference.

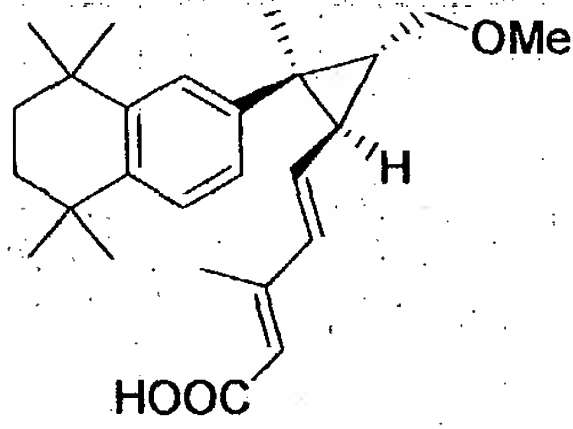
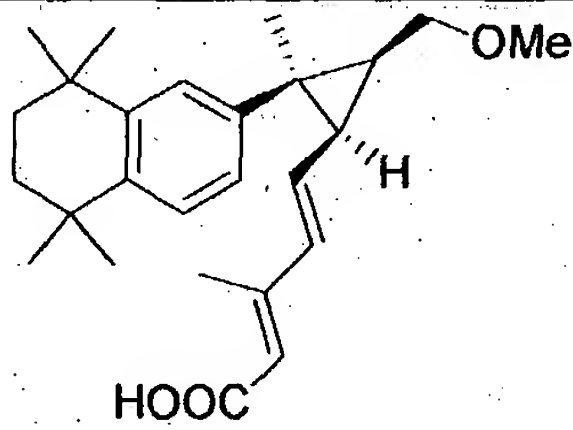
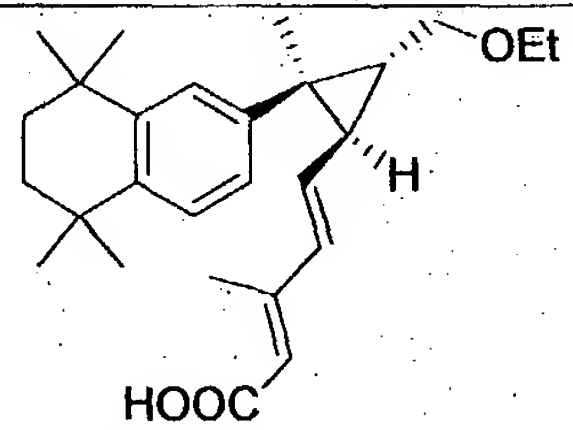
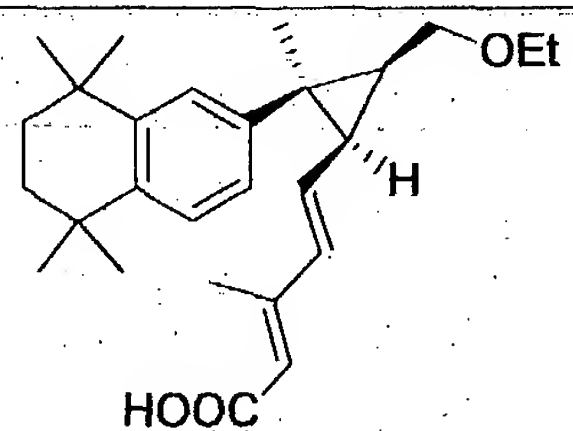
1 **A holoreceptor transactivation assay and a ligand binding assay**
2 which measure the antagonist/agonist like activity of the compounds of the
3 invention, or their ability to bind to the several retinoid receptor subtypes,
4 respectively, are described in published PCT Application No. WO
5 WO93/11755 (particularly on pages 30-33 and 37-41) published on June 24,
6 1993, the specification of which is also incorporated herein by reference. A
7 detailed experimental procedure for holoreceptor transactivations has been
8 described by *Heyman et al. Cell* 68, 397-406, (1992); *Allegretto et al. J.*
9 *Biol. Chem.* 268, 26625-26633, and *Mangelsdorf et al. The Retinoids:*
10 *Biology, Chemistry and Medicine*, pp 319-349, Raven Press Ltd., New
11 York, which are expressly incorporated herein by reference. The results
12 obtained in this assay are expressed in EC₅₀ numbers, as they are also in the
13 **chimeric receptor transactivation assay**. The results of the **ligand**
14 **binding assay** are expressed in K_i numbers. (See *Cheng et al. Biochemical*
15 *Pharmacology* Vol. 22 pp 3099-3108, expressly incorporated herein by
16 reference.)

17 Efficacy in a transactivation assay is expressed as a percentage of the
18 maximum potency attained by the compound compared to a standard which,
19 in this case, is the compound named (2*E*, 4*E*, 1'*S*, 2'*S*)- 3-methyl-5-[2'-
20 methyl-2'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-
21 cyclopropyl]-penta-2,4-dienoic acid. This standard compound is described
22 in United States Patent No. 6,114,533.

23 **Table 1** discloses the activity of certain exemplary
24 tetrahydronaphthale compounds of the invention in the above-described
25 **RXR receptor transactivation and binding assays**. In the chimeric
26 receptor transactivation assay the compounds were essentially inactive in

- 1 activating RAR $_{\alpha}$, RAR $_{\beta}$ and RAR $_{\gamma}$ receptors and these data are not shown.
 2 The transactivation data pertaining to the activation of RXR receptors were
 3 obtained in the holoreceptor assay.

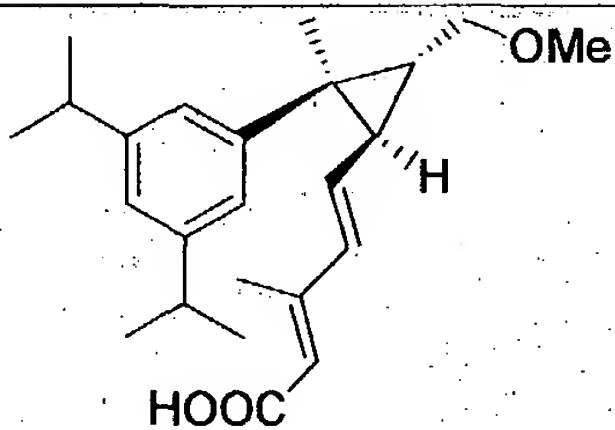
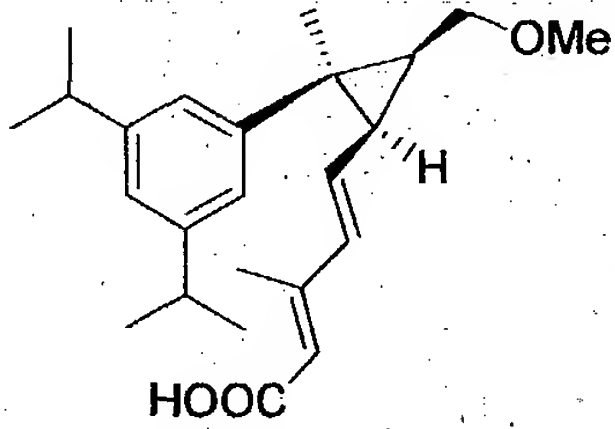
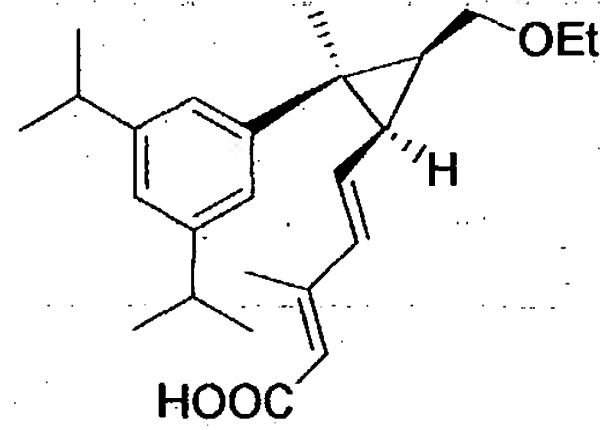
TABLE 1

| Compound # | Structure | Binding (nM) | | | Transactivation (nM) (% Efficiency) | | |
|------------|--------------------------------------------------------------------------------------|--------------|---------|----------|-------------------------------------|------------|------------|
| | | α | β | γ | α | β | γ |
| 23a (-) |  | 18 | 188 | ND | 27 (9) | 546 (9) | 60 (9) |
| 21a (-) |  | 5 | 48 | ND | 4 (39) | 36 (38) | 6 (41) |
| 23b (-) |  | 27 | 121 | ND | NA | NA | NA |
| 21b (-) |  | 17 | 227 | ND | 28 (41) | >1k | 44 (34) |

Note : NA = Not Active; ND = Not Determined

Table 2 discloses the activity of certain exemplary phenyl compounds of the invention in the above-described **RXR receptor transactivation** and **binding assays**. In the chimeric receptor transactivation assay the compounds were essentially inactive in activating RAR $_{\alpha}$, RAR $_{\beta}$ and RAR $_{\gamma}$ receptors and these data are not shown.

TABLE 2

| Compound # | Structure | Binding (nM) | | | Transactivation (nM) (% Efficiency) | | |
|------------|--------------------------------------------------------------------------------------|--------------|---------|----------|-------------------------------------|------------|--------------|
| | | α | β | γ | α | β | γ |
| 29 (-) |  | 11 | 49 | ND | 5 (24) | 47 (34) | 16 (35) |
| 31a (-) |  | 7.6 | 25 | ND | 2.7 (104) | 17 (90) | 3.6 (101) |
| 31b (-) |  | 24 | 96 | ND | 48 (45) | >3k | 4482 (39) |

Note : NA = Not Active; ND = Not Determined

In **Tables 1** and **2** the binding K_i numbers are indicated in the first 3 columns. In the second set of three columns the numbers in parentheses indicate efficacy as a percentage compared to the standard compound, (2*E*, 4*E*, 1'*S*, 2'*S*)- 3-methyl-5-[2'-methyl-2'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-penta-2,4-dienoic acid and the other numbers indicate the measured EC_{50} in nanomolar concentration.

An assay described below tests the effect of compounds of the invention on serum glucose, tryglyceride and thyroxine levels in female 9-10 weeks old db/db mice.

Description of Assay.

Female diabetic *db/db* (9-10 weeks old) mice were maintained on standard laboratory food and treated by oral gavage with vehicle (corn oil), standard compound (2*E*, 4*E*, 1'*S*, 2'*S*)- 3-methyl-5-[2'-methyl-2'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-penta-2,4-dienoic acid (5 mg/kg) or the test compound (5-100 mg/kg, as described in Table 2) daily for seven days at 8:00 AM. Blood samples (70 μ l) were taken by orbital bleeding at 11:00 AM on day 0 (pre-treatment), day 3, and day 6. On day 7, a blood sample (700 μ l) was taken at 11:00 AM and the animals were sacrificed. Glucose, triglyceride and thyroxine (T4) levels were determined on a Boehringer Mannheim Hatachi Clinical Chemistry Analyzer using standard protocols provided by the manufacturer and reagents that were supplied in commercially available kits (glucose and T4: Boehringer Mannheim; triglycerides: Roche Diagnostics). Seven animals were treated in each group. The results of the assays are summarized in **Table 3**.

Table 3

| Treatment (dose) | Glucose (mg/dl) | | | Triglycerides (mg /dl) | | | T4 (µg/dL) |
|-----------------------------------|-----------------|-----------|-----------|------------------------|-----------|-----------|------------|
| | Day 0 | Day 3, 3h | Day 6, 3h | Day 0 | Day 3, 3h | Day 6, 3h | Day 7 |
| Vehicle (Corn oil) | 478 ± 141 | 449 ± 64 | 569 ± 94 | 240 ± 102 | 326 ± 69 | 393 ± 116 | 3.3 ± 0.4 |
| Standard compound (4 mg/kg) | 423 ± 57 | 315 ± 105 | 268 ± 242 | 300 ± 76 | 219 ± 80 | 117 ± 22 | 1.1 ± 0.2 |
| Compound 21a (50 mg/kg) | 445 ± 66 | 339 ± 194 | 314 ± 196 | 271 ± 80 | 130 ± 71 | 180 ± 63 | 4.2 ± 0.3 |

As the data indicate, the compounds of the invention not only cause significant decrease in serum glucose levels and maintain or reduce triglyceride levels in diabetic mammals, but in contrast with the prior art standard compound (2E, 4E, 1'S, 2'S)- 3-methyl-5-[2'-methyl-2'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-penta-2,4-dienoic acid do not have the undesirable side effect of reducing serum thyroxine levels.

MODES OF ADMINISTRATION, DOSING

To treat diabetic mammals, including humans for the purpose of reducing serum glucose levels in said mammals a pharmaceutical composition containing one or more compound of the invention is administered to the mammal in daily doses in the range of 1 to 100 mg per kg body weight of the mammal. Preferably the daily dose is between 10 to 50 mg per kg body weight of the mammal.

Generally speaking the compounds of the invention are also useful for preventing or treating diseases and conditions that are responsive to compounds that promote the expression of or bind to receptors belonging to the steroid or thyroid receptor superfamily. More specifically the

1 compounds of the invention can be used for preventing or treating
2 skin-related diseases, including, without limitation, actinic keratoses, arsenic
3 keratoses, inflammatory and non-inflammatory acne, psoriasis, ichthyoses
4 and other keratinization and hyperproliferative disorders of the skin, eczema,
5 atopic dermatitis, Darriers disease, lichen planus, prevention and reversal of
6 glucocorticoid damage (steroid atrophy), as a topical anti-microbial, as skin
7 anti-pigmentation agents and to treat and reverse the effects of age and photo
8 damage to the skin. The compounds are also useful for the prevention and
9 treatment of metabolic diseases and for prevention and treatment of
10 cancerous and precancerous conditions, including, premalignant and
11 malignant hyperproliferative diseases such as cancers of the breast, skin,
12 prostate, cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx,
13 oral cavity, blood and lymphatic system, metaplasias, dysplasias, neoplasias,
14 leukoplakias and papillomas of the mucous membranes and in the treatment
15 of Kaposi's sarcoma. In addition, the present compounds can be used as
16 agents to treat diseases of the eye, including, without limitation, proliferative
17 vitreoretinopathy (PVR), retinal detachment, dry eye and other
18 corneopathies, as well as in the treatment and prevention of various
19 cardiovascular diseases, including, without limitation, diseases associated
20 with lipid metabolism such as dyslipidemias, prevention of post-angioplasty
21 restenosis and as an agent to increase the level of circulating tissue
22 plasminogen activator (TPA). Other uses for the compounds of the present
23 invention include the prevention and treatment of conditions and diseases
24 associated with Human papilloma virus (HPV), including warts and genital
25 warts, various inflammatory diseases such as pulmonary fibrosis, ileitis,
26 colitis and Kohn's disease, neurodegenerative diseases such as Alzheimer's

1 disease, Parkinson's disease and stroke, improper pituitary function,
2 including insufficient production of growth hormone, modulation of
3 apoptosis, including both the induction of apoptosis and inhibition of T-Cell
4 activated apoptosis, restoration of hair growth, including combination
5 therapies with the present compounds and other agents such as Minoxidil^R,
6 diseases associated with the immune system, including use of the present
7 compounds as immunosuppressants and immunostimulants, modulation of
8 organ transplant rejection and facilitation of wound healing, including
9 modulation of chelosis.

10 To treat diabetes the compounds of this invention are preferably
11 administered, orally.

12 For the prevention or treatment of other diseases or conditions the
13 compounds of the invention may be administered systemically or topically,
14 depending on such considerations as the condition to be treated, need for
15 site-specific treatment, quantity of drug to be administered, and numerous
16 other considerations. Thus, in the treatment of dermatoses, it will generally
17 be preferred to administer the drug topically, though in certain cases such as
18 treatment of severe cystic acne or psoriasis, oral administration may also be
19 used. Any common topical formulation such as a solution, suspension, gel,
20 ointment, or salve and the like may be used. Preparation of such topical
21 formulations are well described in the art of pharmaceutical formulations as
22 exemplified, for example, by Remington's Pharmaceutical Science, Edition
23 17, Mack Publishing Company, Easton, Pennsylvania. For topical
24 application, these compounds could also be administered as a powder or
25 spray, particularly in aerosol form. If the drug is to be administered
26 systemically, it may be confected as a powder, pill, tablet or the like or as a

1 syrup or elixir suitable for oral administration. For intravenous or
2 intraperitoneal administration, the compound will be prepared as a solution
3 or suspension capable of being administered by injection. In certain cases, it
4 may be useful to formulate these compounds by injection. In certain cases,
5 it may be useful to formulate these compounds in suppository form or as
6 extended release formulation for deposit under the skin or intramuscular
7 injection.

8 Other medicaments can be added to such topical formulation for such
9 secondary purposes as treating skin dryness; providing protection against
10 light; other medications for treating dermatoses; medicaments for preventing
11 infection, reducing irritation, inflammation and the like.

12 Treatment of dermatoses or any other indications known or
13 discovered to be susceptible to treatment by retinoic acid-like compounds
14 will be effected by administration of the therapeutically effective dose of one
15 or more compounds of the instant invention. A therapeutic concentration
16 will be that concentration which effects reduction of the particular condition,
17 or retards its expansion. In certain instances, the compound potentially may
18 be used in prophylactic manner to prevent onset of a particular condition.
19 A useful therapeutic or prophylactic concentration will vary from condition
20 to condition and in certain instances may vary with the severity of the
21 condition being treated and the patient's susceptibility to treatment.
22 Accordingly, no single concentration will be uniformly useful, but will
23 require modification depending on the particularities of the disease being
24 treated. Such concentrations can be arrived at through routine
25 experimentation. However, it is anticipated that in the treatment of, for
26 example, acne, or similar dermatoses, that a formulation containing between

1 0.01 and 1.0 milligrams per milliliter of formulation will constitute a
2 therapeutically effective concentration for total application. If administered
3 systemically, an amount between 1 and 50 mg per kg of body weight per day
4 would be expected to effect a therapeutic result in the treatment of many
5 diseases for which these compounds are useful.

6